Canadian Centre for Occupational Health and Safety

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Occupational Exposure Limits: A Discussion of the Issues

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Canadian Centre
for Occupational Health
and Safety

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A Discussion of the Issues

by
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Occupational exposure limits: the concept evolves

Summary

Contemporary industrial hygiene practice is dominated by reference to numerical exposure limits, most often the TLVs published annually by the American Conference of Governmental Industrial Hygienists (ACGIH). Cook, whose 1945 compilation of recommended maximum exposure values drawn from various sources was the immediate precursor of the first TLV list (in 1947), noted a progression in the development of numerical exposure values from standards based on short-term animal exposures, through standards based on observations of long-term exposures of both animals and human beings, to the attempt to relate concentration to duration *via* time-weighted averages.

Numerical exposure limits were not new at the time of Cook's compilation. By 1940, widely accepted numerical values existed for dangerous concentrations of many common gases, based on effects ranging from mild irritation on prolonged exposure to rapidly fatal effects. Many of these values (which reappeared in Cook's 1945 list) were based on German animal experiments dating back as far as the late 1880s, or derived from Flury and Zernik's *Schadliche Gase* (1931). Indeed, some of today's TLVs are based on these same data. A further source of data was a series of short-term (10 minutes up to 11.5 hours) inhalation studies on guinea pigs begun in 1930 by the United States Bureau of Mines.

These and other experiments addressed only the dangers of relatively brief exposures, although they were sometimes used as a basis for intuitive extrapolations of the health effects of longer-term exposures. The first actual studies of long-term effects were carried out on exposed workers in the early decades of the twentieth century. A milestone in the development of such long-term exposure studies, and the parallel decline in industrial medicine's reliance on individual case reports, was a National Safety Council Study on occupational benzene poisoning published in 1927. Its authors used the study as the basis for proposing a maximum allowable concentration of benzene in workplace air, and also undertook one of the first attempts to use biological indicators (white blood cell counts) as indicators of potentially dangerous occupational exposure. A 1936 paper on carbon disulphide inhalation in rats represents one of the first instances in which results from a long-term (20 week) animal study were used — in conjunction with earlier studies of exposed workers — as the basis for a recommended allowable human occupational exposure.

Both these studies were notable for the lack of application of safety factors, and for the *absence* of observed no-effect levels — issues which come up again and again in the later history of numerical exposure limits. The use of animal experiments also created a perceived need for a basis on which to compare human and animal responses. A 1942 study of toluene exposures attempted to develop an empirical basis for relating airborne concentrations to blood levels of toluene and to health effects in both laboratory animals

Summary *continued*

and human volunteers. However, the vexing problem remains to this day of the relative weight to be accorded to animal and human data in setting occupational exposure limits.

Data for permissible exposure limits: a more critical examination

Yet another recurring theme in the history of occupational exposure limits is the degree to which evidence from observations of exposed human subjects (or victims) constitutes the best basis for standard setting. Smyth argued in 1959 that "(t)he best evidence we have...is the accumulated experience of the profession of industrial hygiene," and also noted major inconsistencies in the application of safety factors in the determination of the then-existing TLVs. More recently, Stokinger (a long-time chairman of ACGIH's TLV Committee) noted that 38 percent of the TLVs which had been set as of 1968 "made use of the responses of the industrial workers." However, the data base in question relies at least as heavily on informal observations by, and consultations with, industrial physicians as on systematic epidemiological study.

Whether human beings or animals are being experimented on, central issues with respect to the data on which permissible exposure limits are based include the sensitivity, quality and consistency of the tests or studies used to generate them. Stokinger admitted that, as of 1968, "rather simple and unsophisticated" criteria had been used to develop TLVs. The value of an occupational exposure limit depends crucially on whether it is set with reference to the category of effects to which exposed individuals are most sensitive; this appears often not to be the case. Lack of attention to quality control in tests of laboratory animals appears depressingly widespread even today. Examination of the *TLV Documentation* suggests that flawed experimental design and failure to take into account even health effects (on animals or exposed workers) which were extensively observed in the studies used as the basis for developing exposure limits may seriously compromise some of the TLVs, such as those for acrylamide and hydrogen cyanide.

The enterprise of setting occupational exposure limits has embodied a "quest for certainty"; the result has often been that insufficient attention has been paid to the underlying scientific uncertainties, and to the judgmental elements of standard-setting.

TLVs: the quest for certainty

The axiom that there exists a threshold level for the toxic effects of any substance is traceable directly to Paracelsus' famous dictum concerning the relation between dose and poisoning. However, stating that such a level exists in much simpler than finding out what it is. A biological threshold or no-effect exposure level is

TLVs: the quest for certainty *continued*

not the same as an exposure level below which effects regarded as negligible, tolerable or acceptable.

Today, occupational exposure limits are usually stated as time-weighted average (TWA) exposures over an eight-hour period, corresponding roughly to the length of the working day. At least as early as 1933, this assumption was made in a study of dust exposures which tried to calculate workers' "true average exposure" to dust. This is only a valid approach, however, if the same biological effect is produced by any product of dose and time conceivable on the basis of real workplace exposure levels. Warnings about the weak scientific basis of the TWA concept were frequent in the North American literature in the early postward years, but became harder to find thereafter. Yet Atherley has shown that the TWA remains an assumption, and that only recently have serious efforts been undertaken to test its validity.

Several attempts have been made to take into account the limitations of the TWA concept as applied to TLVs; these include "ceiling" values, short-term exposure limits, and so-called excursion factors for use in calculating the amount by which a TLV may "safely" be exceeded. All these appear to have been chosen arbitrarily, with little scientific basis. Similarly, ACGIH seems to have developed its formulae for assessing the health effects of exposure to combinations of a number of hazardous substances on the basis of assumption (that the combined effects are approximately additive) rather than scientific evidence.

Several factors have contributed to the professional preoccupation with establishing numerical exposure limits, even when the science behind the numbers is questionable. Such limits appear authoritative; they give occupational health and safety professionals a powerful resource in the informal interactions with employers which (at least until the start of the 1970s) were their major opportunity to improve working conditions. The need to refer to such authoritative exposure limits inevitably came into conflict with the need for candor and reflection about the strength of their scientific underpinnings. The comment of an industrial hygienist (in 1956) that numerical exposure limits reduced the "insecurity" of hygienists by providing a "*scientific* basis for consideration of alternative control strategies" stands as an evocative instance of this ascription of authority to numbers.

Health, risk and acceptability

The concept of a "threshold" as applied to occupational exposure limits may have an important social function because it embodies an implied definition of health, by way of a distinction between effects on health and physiological changes (presumed to be) without medical significance. As early as 1950, this distinction was accepted by North American industrial hygienists and

Health, risk and acceptability *continued*

physicians. Hatch was subsequently (1962) to codify the distinction in terms of an "impairment-disability curve"; this concept has been widely accepted, as in a 1975 World Health Organization report which emphasized that "a statistically significant (physiological) effect as such is not the same as impairment of health".

Defining health (and thus, adverse health effects) emerges as a social process. Contrasted definitions of health, particularly with reference to behavioral toxicity, appear to be important in explaining the substantially lower exposure levels for certain types of substances considered permissible in the USSR, in comparison with North American values. Without reference to Soviet exposure limits, a dramatic illustration of this point is provided by the history of the TLV for airborne lead. Today's TLV derives from a 1933 study which suggested only that the limit would be sufficient to avoid severe lead poisoning. Subsequently, the use of blood lead levels as indicators of exposure or uptake became widely accepted. More recently, blood lead levels of 70 or 80 ug/100 ml have been considered acceptable only because a number of physiological effects on the nervous system have not been considered, in ACGIH's words, as "incompatible with good health". Such judgments go beyond both the science of toxicology and the art of diagnosticians; they are social artifacts, not scientific conclusions.

Risks, benefits and 'acceptable risk'

One interpretation of the history of standard-setting is that we have gradually become more sensitive to the degree of physiological alteration or impairment which is regarded as acceptable. Smyth, writing in 1979, noted that because "adverse reactions (to benzene exposure) in one-third of those exposed is no longer acceptable," the TLV had been lowered over four decades by a factor of ten. The social nature of such acceptable risk decisions is illustrated by two distinct processes.

One is the choice of exposure standards on the basis of a decision to accept a specified statistical risk as the maximum which should be considered acceptable. The figure is normally chosen based on a comparison with risks from other workplace hazards; the International Commission on Radiological Protection (ICRP) has adopted this approach in its recommended standards for radiation exposure. More often, it is claimed that risks to workers should be judged in terms of corresponding benefits to "society".

Such a cost- or risk-benefit perspective is often incorporated informally in occupational exposure limits, and becomes particularly important when the issue is that of how much evidence should exist for a suspected health effect—that is, the choice of a standard of proof. The extensive consultation with industry

Risks, benefits and 'acceptable risk' *continued*

carried out by ACGIH's TLV committee embodies an institutional bias in favor of setting high standards of proof, and correspondingly limiting the costs to industry of achieving the stated exposure limits, but the risk-benefit comparisons implicit in the standards which emerge remain inscrutable. If the definition of health is not actually a function of what people in industry feel they can afford at a specific point in time, it becomes important in that context.

Standards for occupational exposure to suspect carcinogens illustrate the many dimensions of acceptable risk decisions. Deciding what should and should not be considered a carcinogen is itself a subject of considerable controversy with respect to the relative weight accorded to animal and human evidence. The International Agency for Research on Cancer (IARC) treats substances which are clearly carcinogenic in animal experiments as if they presented a carcinogenic risk to human beings, but emphasizes that this is a policy decision and not a scientific conclusion. Other standard-setting bodies, like ACGIH, place greater emphasis on the need for human evidence. Yet epidemiological evidence is in many instances all but impossible to obtain. Carcinogens also raise once again the issue of thresholds. They so-called mega-mouse experiment failed to demonstrate the existence of biological no-effect levels; thus *any* level of exposure to an occupational carcinogen represents acceptance of a finite (even if minute) additional risk. Examples drawn from the *TLV Documentation* suggest that the scientific basis of ACGIH's approach to setting TLVs for suspect carcinogens is questionable; the approach is also internally inconsistent.

Standards for the individual workers: safe-person strategies

The focus of contemporary industrial hygiene is shifting from working conditions to the individual exposed worker. Recommendations that workers be monitored to detect uptake or effects of toxic substances are nothing new, as illustrated by the National Safety Council study on benzene. Nor is attempting to determine the characteristics of the worker, for purposes of selecting physically or physiologically suitable individuals, a recent practice.

An important conceptual step in this respect was Hatch's 1962 argument that "a point may be reached...where the risk of ill health depends more on the status of the host than it does on the conditions of exposure." In that same year, Stokinger and others began extensive efforts to promote biological monitoring techniques aimed at detecting the "hypersusceptible" worker. The theoretical attractiveness of biological monitoring is clear: it allows for individual variations in response to, and uptake of, workplace contaminants. It also provides information based on *total*, rather than work-specific, exposures. Yet ACGIH's use of biological indicators to determine acceptable levels of carbon monoxide

Standards for the individual workers: safe-person strategies *continued*

exposure shows, once again, that such determination are social rather than scientific—for biological thresholds in this case, as in others, are conspicuous by their absence.

A more basic point is that of the definition of hypersusceptibility: what percentage of the exposed population do we wish to protect? This question cannot be answered on scientific grounds. The published literature confirms the suspicion that the rationale for increased reliance on safe-person strategies was (and is) largely economic. Screening relatively vulnerable workers involves little cost to industry apart from the cost of the screening process itself. And a shift of emphasis in setting permissible exposure levels from environmental to biological indicators may lend added credibility to the continuation of the human experiment which has characterized past practices in industrial hygiene and occupational standard-setting.

Occupational exposure limits: the concept evolves

Introduction

Whether they work for industry or for government, most professionals and technicians in the field of workplace health today assess the dangers posed by effects of airborne contaminants on the basis of supposedly authoritative numerical exposure limits. Especially in North America, the most widely used values are the Threshold Limit Values (TLVs) promulgated by the American Conference of Governmental Industrial Hygienists (ACGIH). Most Canadian jurisdictions have in place a set of official exposure limits derived, sometimes with minor variation, from the ACGIH values. These limits are, in theory at least, legally enforceable since they are embodied in regulations. Yet the fact that these limits have been entrenched in law is probably less important, in terms of their impact on working conditions, than the importance attached to these limits by government, industry, and the scientific/technical community. Louch (1, p.2) said in 1982 that "it is fair to say that the regulation of chemical exposure in Canadian workplaces is done by ACGIH."

This extensive reliance on numerical exposure limits, which is of course not exclusively a North American phenomenon, is the rationale for the present report which looks, in a preliminary way, at the data and assumptions underlying numerical exposure limits and the uncertainties which pervade the setting of such limits.

Warren Cook (2) has described the development of occupational exposure standards in the United States in three phases:

- the development of standards based on short-term animal exposures;
- the move to standards based on long-term exposures, both of animals and of human beings; and

Introduction
continued

- the "relation of concentration to duration" through the development of time-weighted averages.

Cook is not just an observer. He was one of the most influential individuals in the development of exposure limits in North America; among his contributions (3) was the publication in 1945 of a list of "accepted and tentative values based on industrial experience, animal experimentation, sensory responses of persons, or a combination of these". The list documented the basis for each of these values and compared them with values in use in by the relevant authorities in a number of American jurisdictions (including California, Connecticut, Massachusetts, New York, Oregon and Utah) on an official or semi-official basis. Cook's 1945 list was the immediate precursor of the first published ACGIH list of occupational exposure limits, which appeared in 1947. His observations are therefore useful as a participant's view of the influences on the development of such limits, and they form the framework for this section of the report.

Cook's view of the significance of data on the effects of short-term exposures in determing permissible exposures is shared by H.B. Elkins, a hygienist who spent approximately 40 years with Massachusetts' Department of Labor. Speaking in 1978, Elkins noted that:

> "The concept of TLV's was not new in 1940. All the old text-books on the toxicology of gases contain tables indicating concentrations which are dangerous in one hour, etc., and those which can be inhaled for prolonged periods without ill effect. As a matter of fact the current TLV for aniline appears to be based mainly on such a statement in Henderson and Haggard's 'Noxious Gases,' first published around 1927." (4, p. 84)

The 1943 revised edition of Henderson and Haggard does indeed contain numerous such tables. The section on irritant gases deals with physiological responses to various concentrations of ammonia, hydrochloric acid gas, hydrofluoric acid gas, sulphur dioxide, chlorine, bromine, iodine, phosphorus trichloride, and phosgene. The effects included range from mild irritation on prolonged exposure to rapidly fatal effects (5, pp 110-141). The classification of effects used in the table on chlorine is typical. The headings are: maximum concentration allowable for prolonged exposure; least detectable odor; maximum concentration allowable for short exposure (1/2 to 1 hour); least amount causing immediate irritation to the throat; dangerous for even short exposure; and, rapidly fatal for short exposure. A table in a later chapter (p. 201) compares physiological responses to various concentrations of halogenated hydrocarbons, under the following headings: estimated allowable concentration for prolonged exposure; slight symptoms after exposure for eight hours; deep narcosis, 30 minutes; kills animals in a short time.

Introduction
continued

According to Cook, the basis for setting allowable concentrations of toxic substances in air based on short-term animal exposures can be traced to Gruber's 1883 publication (6) of the results of exposing animals to carbon monoxide at various concentrations. These experiments led Gruber to conclude that "the limit of noxiousness for carbon monoxide is in all probability at a dilution of 0.05, but certainly at a dilution of 0.02 percent" (for example, at 500 or certainly at 200 ppm). Gruber claimed to have confirmed this lower limit with short-term tests using himself as the experimental subject; he failed to show any adverse reaction to CO at 0.02 percent (roughly) for three consecutive days.

Cook describes as "a remarkable series of short-term animal experimentations, resulting in basic data for occupational exposure standards of a wide variety of toxic substances," the series of investigations conducted by Lehmann *et al.* at Munich's Hygenic Institute. The first report of these investigations appeared in 1886; the last (dealing with chlorinated hydrocarbons), in 1936. Cook's observations are not the only indication of the importance of German science in the years before the late 1930s in assessing the effects of hazardous substances in the workplace. Alice Hamilton (7, p. 587) wrote in 1929 that:

> "Before the [First World] War we could trust to the Germans to test on animals every new compound used in industry, and we could follow their results; but German universities no longer have the money for such researches ..."

Her autobiography, published in 1943, reveals that this European influence extended to the broader area of occupational medicine. When Hamilton first became interested in work-related diseases she attempted

> "...to read everything [she] could find on the dangers to industrial workers, and what could be done to protect them. But it was all German, or British, Austrian, Dutch, Swiss, even Italian or Spanish — everything but American. In those countries industrial medicine was a recognized branch of the medical sciences; in my own country it did not exist. When I talked to my medical friends about the strange silence on this subject in American medical magazines and textbooks, I gained the impression that here was a subject tainted with Socialism or with feminine sentimentality for the poor." (8, p. 115)

Another German influence not specifically mentioned by Cook was Flury and Zernik's *Schadliche Gase*, published in Berlin in 1931 — an influence which continues to this day. For example, the table listing the effects of acute exposures to various concentrations of hydrogen cyanide, which appears in today's *TLV Documentation* as the basis for the ceiling limit of 10 ppm, is taken directly from

Introduction *continued*

Schadliche Gase, with one minor exception (as reproduced in 9, p. 15). Yet another indication of the extent of German activity in the field is provided in von Oettingen's extensively documented 1937 review of "The Halogenated Hydrocarbons: Their Toxicity and Potential Dangers" (10). Of 319 references cited by von Oettingen, 141 were from German journals or other German-language sources.

A further substantial contribution to the development of occupational exposure limits, as judged on the basis both of Cook's 1945 compilation and of the extent to which they are referred to by von Oettingen (10), was provided by a series of American experiments. These tests of the effects on guinea pigs of inhalation of various substances, for periods ranging from 10 minutes up to 11 or 11.5 hours, were conducted under the auspices of the U.S. Bureau of Mines and published in the U.S. government's *Public Health Reports* between 1930 and 1938. The substances tested included ethyl benzene (11); "Cellosolve", a tradename for ethylene glycol monoethyl ether (12); ethylene oxide (13); vinyl chloride; 1,4-dioxan (14); methyl ethyl ketone (15); methyl propyl ketone (16); methyl butyl ketone (17); secondary amyl acetate (18); and methyl formate (19). The results of these tests were extensively cited in subsequent reviews of available information.

Lehmann's experiments provided the basis for two values in Cook's 1945 listing, and were cited (but were not the determining or limiting values) in the documentation for two others.

Exposure limits proposed or cited in *Schadliche Gase* were cited as a basis for eight values. According to Cook (2, p. 273):

> "[I]n the latter twenties it was suggested as a rule of thumb that, where a given concentration was safe for eight hours, the acceptable concentration for weeks or months might be taken as a fourth of the eight-hour value."

A version of this practice persisted well after the 1920s, despite warnings such as that provided by Henderson and Haggard (5, p. 200) that "[s]ome of the halogenated hydrocarbons which kill animals after only 1 hour in very high concentrations may have far lower permissible concentrations for the prolonged exposure of men than do others which cause acute fatal poisoning in comparatively low concentrations." This warning was to be echoed in 1955 by Sterner (20, p. 28), who commented that "the single threshold limit does little to define the relative hazard of substances with respect to acute or chronic effects ... "

In Cook's 1945 compilation, the values derived in the Bureau of Mines' tests for acute exposures were cited eight times as the basis for proposed limits on chronic exposures, usually with the application of the same arbitrarily chosen four-fold safety factor.

Introduction *continued*

In four other cases, the work of this group was cited, but other evidence of effects at lower concentrations than those used in the Bureau of Mines tests was used as the basis for proposed exposure limits.

One of the interesting features of the approach taken in the Bureau of Mines' experiments was the graphing of the concentration to which test animals were exposed (on the vertical axis) against the time of exposure (horizontal axis). The response of each group of test animals (for example, the group exposed to concentration x for time y) was located on the graph, on the basis of a classification of the type of effects observed during the test (for example, death) and afterwards (on the basis of examination for gross changes in the organs of the test animals). The classifications strongly resemble those in the tables published by Henderson and Haggard. The effect of this procedure, two examples of which are illustrated in Figures 1 and 2, was to create the basis for a rough estimate of "zones of toxicity" corresponding to the effects of various products of concentration x time for *acute* (short-term) exposures, on the basis of an admittedly limited number of observations.

From short-term to long-term studies

Cook notes that the first studies of the effects of long-term exposure to toxic substances in an occupational context were carried out using human subjects, beginning with correlations between dust high in free silica and the lung X-rays of South African miners, and with studies of lead and zinc miners in the United States in the second decade of the 20th century. Like other authors, he goes on to cite the National Safety Council's study of occupational benzene poisoning in the 1920s as a landmark in the assessment of the effects of long-term exposures.

In his summary of the results of that study, Winslow (21) noted the extent to which it represented a departure from previous approaches.

> "Nearly all previous work on industrial poisons has been of what may be termed a qualitative type. It has dealt with a relatively small number of instances of poisoning which have come, one by one, to the notice of physicians, and such cases, from the nature of the situation, have been as a rule of a more or less aggravated type."

The qualitative nature of much of the then-available information on human industrial poisoning is amply illustrated by the heavy reliance on case reports in Hamilton's *Industrial Poisons in the United States* (22), published in 1925. This reliance on case reports does not mean that investigations of industrial poisoning even in the United States had been unsystematic. For example, Illinois

Figure 1

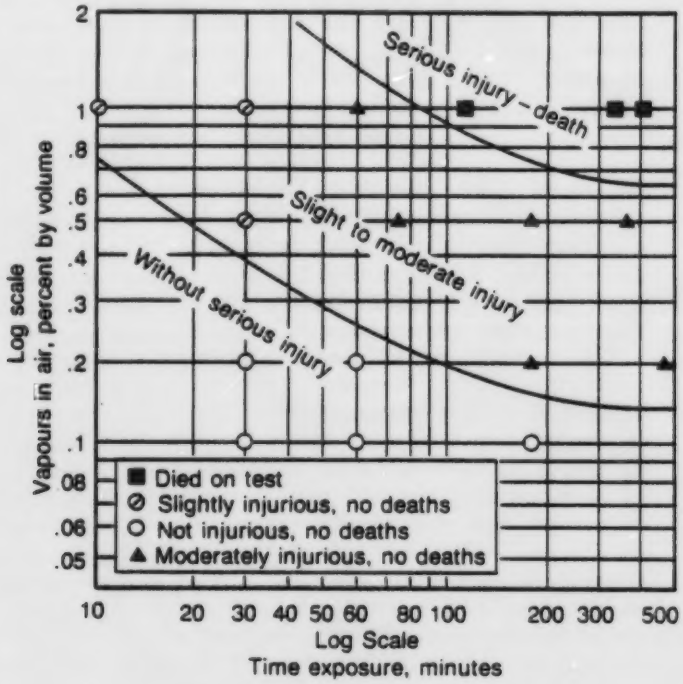
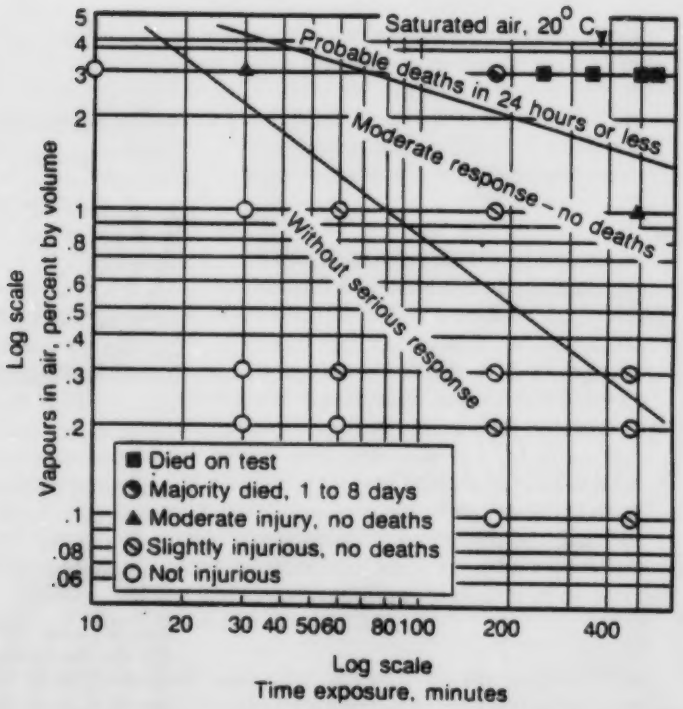


Figure 2



From short-term to long-term studies *continued*

had set up a Governor's commission to investigate industrial poisoning in 1910. An earlier federal survey had revealed the existence of more than 150 cases of phosphorus poisoning among workers in match companies; the Illinois survey was followed by a federal survey which began in 1912 (7, 8).

The distinctive nature of the National Safety Council study lay rather in its

> "...conscious and definite effort to pick out a representaive group of *apparently normal* workers in a given industry and to make a quantitative study of:
> (a) Mechanical conditions affecting a possible poison hazard:
> (b) Analytic data indicating the degree of atmospheric pollution by the poison in question; and
> (c) Physical findings including delicate chemical, microscopic, and physiologic tests suitable for the detection of latent and incipient damage to the human body such as threatens the subsequent development of active clinical disease." (21, p. 62; emphasis added)

Atmospheric sampling of workplace air indicated average benzene concentrations as shown in the table below.

Workplace conditions	Benzene levels (ppm)
Small amounts of benzene in use; no ventilation (or general ventilation only)	100 - 1360
Large amounts of benzene in use; no ventilation (or general ventilation only)	340 - 1800
Large amounts of benzene in use, with enclosed systems of local exhaust ventilation	70 - 500*

A white blood cell count below 5500 per cubic millimetre of blood (as against a specified normal value of 7500 to 9000) was used as the first indicator of early chronic benzene poisoning. Use of this criterion represented an early instance of a trend which (as noted in the final chapter of the present report) was later to become far more widespread: the use of biological indices as the initial indicators or determinants of adverse effects on human health. Blood tests on 81 exposed workers indicated that 32 per cent of them showed clear evidence of blood cell destruction, evidence not found in any of 50 unexposed controls. Evidence of poisoning

*in the best-ventilated operation, 70-90 ppm

From short-term to long-term studies *continued*

was most prevalent in workplaces where large amounts of benzene were used without local ventilation (10 of 19 workers showed evidence of poisoning). Even in the operations with good local exhaust ventilation one-fifth of workers examined showed evidence of poisoning. The study concluded that

> "...the control of the benzol hazard (except where the substance is used in completely closed systems) is exceedingly difficult; that, in practice, systems of exhaust ventilation capable of keeping the concentration of benzol in the atmosphere below 100 parts per million are extremely rare: and that, even when this is accomplished, there remains a decreased, but substantial, hazard of benzol poisoning."

More than a decade later, a Massachusetts study of 89 benzene workers (23, 24) included 10 fatal cases of benzene poisoning, two of which were estimated to result from exposure to average concentrations well below 75 ppm, "indicating the possibility of occasional cases of benzene poisoning with even the best of control" (23, p. 330). The study also strongly criticized reliance on white blood cell counts as the most sensitive diagnostic criterion for benzene poisoning, noting that an abnormal white blood cell count was always accompanied by other abnormalities in the workers examined, and that normal counts might contribute to a false sense of security (24).

These studies are noteworthy not least because, in 1945, Cook cited them as the basis for his conclusion that, despite a semi-official maximum exposure limit of 100 ppm, exposures should be kept below 50 ppm. The current TLV of 10 ppm is said by ACGIH to provide a "safety factor" since there is little evidence of any blood abnormalities among workers exposed at concentrations below 25 ppm.

In 1936, Wiley, Hueper and von Oettingen published the results of a study of the effects of inhalation of carbon disulphide on rats and mice exposed eight hours a day, five days a week for 20 weeks; selected animals were sacrificed and autopsied at various points during the study. At an average concentration of 1.09 mg/litre of air, the rats showed testicular degeneration, and the mice showed hepatic degeneration. Irritation of the intestinal tract and damage to the central nervous system were also observed. At an average concentration of 0.114 mg/liter of air, test animals showed damage to the brain, liver and kidneys and irritation of the intestinal tract. The report of these experiments recommended that the concentration of carbon disulphide in work areas be kept below 0.1 mg/litre, and that higher concentrations be dealt with by work practice controls to limit exposure (25).

The recommendation was based not only on the results of the animal experiments, but also on a number of earlier studies, cited

From short-term to long-term studies
continued

in the report, of the effects on workers of chronic exposure to carbon disulphide. One of these, a study of exposed workers in the German rubber industry, found that of 57 workers exposed to concentrations less than 1 mg/litre, and sometimes as low as 0.1 mg/litre, only six

> "...were subjectively and objectively normal. The remaining fifty-one had been employed in these operations for periods between 5 months and 20 years. Seven complained of loss of appetite, gastro-intestinal disturbances, headache, loss of libido, excitement and depression. Four suffered from polyuria, eleven from loss of appetite, sixteen from gastric disturbances, nineteen from intestinal disfunctions, especially constipation, twenty-two complained of nausea, vomiting, and headache, fourteen suffered from forgetfulness and loss of memory, and *thirty-eight suffered from slight visual disturbances.*" (25, p. 739: emphasis in original. This is Wiley *et al.*'s summary of the results of the study, which was published in German.)

Wiley *et al.* also noted evidence from the literature on human exposures that carbon disulphide acts as a sensitizer even in cases of "moderate poisoning."

The studies of benzene by the National Safety Council, and of carbon disulphide by Wiley *et al.*, differ in that the former was conducted principally on human subjects and the latter, on experimental animals, although its recommendations were based on human experience as well. Yet both are noteworthy for (a) the *lack* of the application of a safety factor to the results of the study, and (b) the *absence* of a demonstrated no-effect level. Recommendations for maximum human exposures are based, instead, on approximate comparisons with concentrations of airborne contaminants which *had* produced discernible (in the case of benzene, sometimes disastrous) adverse effects in the organisms being studied. One of several promising areas for future research involves a systematic inquiry into the process by which such conclusions were subsequently taken to represent "safe levels" without detailed scrutiny of the conditions under which the study's conclusions were reached.

To leap forward in time for a moment, an example which suggests that this process may be significant with respect to a number of substances concerns the current TLV for acetaldehyde. The TLV of 100 ppm is recommended to prevent excessive eye irritation and potential injury to the respiratory tract, based largely on the work of Silverman *et al.* which showed — according to the TLV Documentation — that unacclimated subjects "at first experienced some eye irritation at 50 ppm, but the majority were willing to work an 8-hour day in 200 ppm ... ." (26, p. 3). The original (1946) source, however, says:

From short-term to long-term studies *continued*

> "A majority of subjects were willing to work an 8-hour day in 200 ppm of acetaldehyde. Eye irritation, however, appears at 50 ppm, and several subjects objected to this material strenuously even at 25 ppm. We therefore believe that the sensory limit should be 50 ppm or less." (27, p. 265)

The theoretical point here is that failing to consider all the circumstances and conclusions under which proposals for exposure limits were arrived at in experimental studies, be they on animals or human beings, can lead to drastic underprotection of workers exposed as a result of adherence to such limits.

To return to the case of carbon disulphide, Gordy and Trumper noted in 1938 (28, p. 1549) that "[u]ntil a few years ago, most authorities relied on the quantitative experimental work of Lehmann on animals" — work which was restricted to the effects of eight- or nine-hour exposures. They cite the work of Wiley *et al.* as well as the "many hundred" reported cases of carbon disulphide poisoning (including six within their own experience) as the basis for recommending that concentrations in the workplace be kept below 0.03 mg/l (10 ppm).

Unlike many other authors of the period (and for that matter of later years), Gordy and Trumper pointed out that extrapolating the results from animal tests of suspected neurotoxins to human exposures is complicated by the problem of scale. "Human neural tissue with its vascular supply is capable of absorbing a relatively greater quantity of circulating neurotoxin than the nervous system of animals." Animals, except apes or *conditioned animals*, cannot exhibit psychopathologic changes. Thus, "[t]he vast panorama of neuropsychiatric symptomatology...can only be partially illuminated by animal intoxication." (28, p. 1549: emphasis added)

The point of this section of the report is to indicate some analytical issues of historical and contemporary importance in the setting of occupational exposure limits. To understand these questions, it is important to consider the perceived need to establish a basis for comparing results of animal and human exposures. In 1949, Schrenk (29, p. 58) noted that the "important disadvantage" of using laboratory tests on animals as the basis for establishing permissible concentrations is that "it is not possible to interpret such data in terms of human response with a high degree of accuracy."

The question of verification, on the basis of human exposures, of exposure limits based on animal data was explicitly addressed at least as early as 1942, when von Oettingen and co-investigators published the results (30) of a series of investigations aimed specifically at setting a "maximal permissible concentration" for the solvent toluene in workplace air. Tests were conducted initially on three human volunteers over roughly three months, using

From short-term to long-term studies *continued*

concentrations ranging from 50 to 800 ppm over an eight-hour period, with half an hour without exposure to simulate a normal lunch hour. "[N]ot more than two experiments were performed per week, in order that there should be sufficient time between experiments for recovery." On the basis of subjective and objective symptoms, the experimenters concluded that "definite impairment of certain nervous functions" occurred at 200 ppm over an eight-hour day; subjects did have some subjective complaints at lower levels, however, especially when exposure at 100 ppm occurred following an exposure to 800 ppm.

Levels of toluene in the blood of volunteers correlated well with air concentrations, with the concentration in the blood of volunteers exposed to 200 ppm being roughly 0.5 mg/100 cc. of blood.

> "In order to find out to what extent these values could be duplicated in dogs, three dogs were exposed in one experiment...simultaneously with the human subjects to concentrations of 300 ppm of toluene in air, and the concentration of toluene in their blood was determined at the end of the experiment. This was found in two animals to be 0.74 and 0.79 mg. per 100 cc. of blood, and in the third, in which the sample was smaller than usual, 1.04 mg per 100 cc. These first two values check very well with the 0.73 mg. per 100 cc. which was found with humans in the same experiment. It appears, therefore, that dogs can be utilized very well for such determinations." (30, p. 14)

Von Oettingen *et al.* found the effects on the human nervous system to be the limiting (that is, most sensitive) parameter, and therefore recommended a permissible exposure limit of 200 ppm for eight hours' exposure daily, with the warning that "[i]n operations which offer specific accident hazards this concentration may prove to be too high" because of the impairments shown in volunteers even at lower exposure levels. The study did not address explicitly the potential long-term effects of exposure at concentrations lower than those studied, but without an opportunity for recovery between experimental exposures. Nevertheless, it is interesting as an attempt to build correlations between animal and human biological indicators into the design of a single study.

This introductory look at the data underlying permissible exposure limits has examined some early attempts to use animal data to develop standards for workplace contaminant exposures. The chapter which follows looks in greater detail at this enterprise, and at the relative weights which have been afforded to animal and human data in the setting of occupational exposure limits.

Data for occupational exposure limits: a more critical examination

Sources of data

One of the themes which recurs in discussions of occupational exposure limits, as in debates over standards for exposure to toxic substances in other situations, is the degree to which evidence from observations of exposed human subjects (or victims) constitutes the ideal basis for standard-setting. Henry Smyth, writing in 1959, argued

> "[T]he ideal basis for defining the greatest concentration of a respirable substance which should be in the working environment is the prolonged critical examination of several considerable groups of workmen exposed to different constantly monitored concentrations. ...we are slowly approximating the ideal for the more widely used substances by the accretion of observations made during industrial operations." (31, p. 341)

These observations began an article in which Smyth undertook to assess the worth of animal experiments in setting TLVs in the light of subsequent industrial experience. With this objective in mind, he examined the sources of information used to set TLVs for all substances for which TLVs were first proposed in 1953 or earlier, on the assumption that "any substance which has appeared in lists of threshold limits for at least five years is considered to have had sufficient observation in industrial use to be regarded as reasonably well understood."

The investigation aside, Smyth's statement is interesting in itself, since it suggests he would expect no revisions of a TLV to take place more than five years after its initial proposal, except on the basis of changing definitions of health or improved analytical techniques. This proposition is certainly debatable with respect to carcinogens, whose effects on exposed human beings may not become evident (especially not in a statistically signficant manner) for two decades. It also assumes an extremely high degree of accuracy and comprehensiveness in the feedback provided by the experience of those setting TLVs. The mechanism of validation is internal and represents to a considerable degree a closed system. This comment is not merely a conjecture; it is confirmed by Smyth's statement that "[t]he best information we have...is the accumulated experience of the profession of industrial hygiene, expressed in the annually revised list of threshold limits" (31, p. 341). In contrast, Henschler noted 25 years later that:

> "If we look back on changes in exposure limits in the course of the past 10-15 yr, we see that the existing limits usually were lowered, often in a sequence of steps. With some compounds, these decreases have been dramatic...And if we review those values which have remained constant over more than 10-20 yr, it becomes clear that in most cases nobody has reassessed them. Therefore, lack of change is by no means indicative of a satisfactory probation." (32, p. 69)

Sources of data
continued

Smyth found that the original TLVs for 45 of the substances he considered had been set on the basis of repeated inhalation or feeding studies in animals; 34, on the basis of single inhalations or injections (again using animals); 26, on the basis of human experience and surveys; 26, on the basis of human experiments (presumably short-term ones involving volunteers); 17, on the basis of analogy with better-known substances. Changes had been made to 18 TLVs originally based on repeated administration to animals, of which eight were based on subsequent human observations, but only one on the basis of a systematic epidemiological study. The "industrial experience", which many authors have described as an essential if not unique ingredient of TLVs, was at least at that time derived not from epidemiological studies but rather from the operational experience of individual company physicians and industrial hygienists.

Another significant conclusion of Smyth's examination of the later history of the TLVs first set in 1953 is that there was

> "...a very wide range of conservatism displayed in the relation between the threshold limit proposed and the results of repeated inhalation by animals. If we define the safety factor as the greatest concentration which had no effect on animals, divided by the proposed threshold limit, the safety factors ranged from 0.2 to 10."

In 1955, Sterner (20, p. 28) had similarly commented on "the relative inequality of threshold limit values," as indicated by the disparity among safety factors applied to various substances. These comments are especially significant in view of the observations made earlier about experimental designs which failed to observe a no-effect level on animals, and of Stokinger's considerably later (1970) observation that:

> "It is not uncommon to find that the 'no-effect' level is one-fifth, or one-tenth, or less that at which minimal efects occur. The magnitude of the spread between the two levels depends upon the rate of change in exposure level (damage) or the slope of the response curve. Some estimate of the slope may be gained from the observed spread between the level giving frank effect and that giving minimal change." (33, p. 41)

Smyth found a tendency for limits which had been changed between 1953 and 1958 to incorporate smaller safety factors than those which had not been changed. Stokinger noted in 1972 that the choice of safety factor "depends upon the seriousness of the response" and that safety factors "are all judgmental values derived from the long experience of the TLV Committee members." (34, p. 156) Unfortunately, Smyth did not indicate whether and how safety factors had been applied in the case of the TLVs originally set on the basis of single inhalation or injection studies

Sources of data *continued*

in animals or in human experiments. Nor did he indicate the basis for the frequent changes in TLVs set on information other than results of repeated inhalation or feeding studies.

It is essential to recall that the "spread" with respect to the effects of single exposures, as indicated by the graphs produced in the U.S. Bureau of Mines studies, appears to *change considerably* for some substances — that is, it was not found comparable at all tested combinations of concentration and time. This phenomenon has important implications for the concept of time-weighted average. Atherley (35) has shown that the equation of dose with the product of concentration (of an airborne substance) and the duration of exposure, the essential assumption behind the use of time-weighted average as the basis for setting exposure limits, has not been scientifically validated and should probably be treated as nothing more than an assumption. Chapter 3 of this report suggests that the lack of an empirical basis for this equation was recognized almost four decades ago, but that the resulting uncertainties were downplayed because of the perceived need for authoritative exposure limits.

In a more recent examination of the sources of information on which TLVs are based, Stokinger (33, 36) noted with respect to the 414 TLVs which had been set as of 1968 that:

> "38 per cent made use of the responses of the industrial worker, and that chronic animal inhalation studies were employed about half as frequently (20 per cent). It is interesting to note that the development of TLVs by analogy accounted for about one-quarter of the procedures used. Human volunteer studies were responsible for about 1 in 10 of the limits, and the remaining animal procedures other than chronic inhalation accounted for but about 1 in 14 limits." (33, p. 39)

Under industrial plant experience are included epidemiological studies and medical surveillance. "Here," notes Stokinger,

> "...is a place that the industrial plant physician can be of real help in supplying data through good medical records, but only if combined with *simultaneously obtained environmental data.*" (36, p. 278; emphasis in original)

Using exposed workers as a source of data is, of course, hardly a new procedure, even when combined with environmental monitoring. Silson noted in 1949 that:

> "When one or more workers become ill from an exposure which can be determined, an upper limit is established, and a tentative MAC can be set sufficiently below that limit to allow an adequate margin of safety. When a group of workers have been shown to tolerate a determined exposure for an adequate

Sources of data
continued

length of time with no toxic signs or symptoms, this can be assumed as a safe exposure. Further information is sometimes obtained by surveying a group of workers for medical evidence of poisoning while simultaneously studying the air contamination." (37, p. 6)

The subsequent literature is replete with insistences on the need for validation by human experience of exposure limits originally suggested by animal experiments. As one example, Irish (38, p. 549) observed in 1965 that:

> "Animal investigations in the toxicological laboratories are becoming more definitive both qualitatively and quantitatively. We can also develop a better understanding of the biological and biochemical mechanisms involved. With this information, we can make tentative suggestions for several allowable levels in the work environment. If men are working in such an environment, we need to obtain a good analysis of the concentration in the work space and in work time. ...This information should be supplemented where possible with biochemical analysis of blood, urine, expired air, or the like, from the exposed men. Next, the clinic should evaluate the 'state of health' of the men in that environment. The relation of the 'state of health' to the pattern of potential exposure plus the toxicological information should give us a basis for evaluating the criteria for and the boundaries of a healthful work environment."

As an example of how such data have been used more recently in the validation (re-examination and evaluation) of TLVs by the ACGIH Committee, Stokinger (who was then its Chairman) commented in 1969 that

> "...a most productive day's meeting was held with industrial physicians and hygienists of the chromate industry. The reason for selecting the chromate industry was that no evidence of the suitability of the TLV for chromic acid or chromates had ever been brought forth for the prevention of either nasal perforation or bronchogenic carcinoma. All environmental levels had exceeded the recommended limit of 0.1 mg/cu.m. when large excesses (29-fold) of lung cancer and nasal perforation were found in 1950, and the health experience had not been reviewed in these terms since the industry had improved its control measures to the recommended limit. In brief, the day's discussion revealed that the limit for chromic acid mist was satisfactory in preventing nasal perforation, and in addition contained a safety factor of three or four; that the limit was probably satisfactory for the prevention of lung cancer, as no new cases have appeared since the reduction in exposure occurred, but that the ten years in which the closer

Sources of data *continued*

controls are operative are probably too short a time to be certain of its validity in this respect." (36, p. 279)

Sterner, a physician, is one of the few professionals in the field of industrial hygiene who have acknowledged the extent to which determination of allowable exposures on the basis of evidence of this sort represents an experiment on human subjects. In a 1955 lecture on "The Experimental Animal — Man — in Industrial Hygiene," he pointed out that man

> "...has been an experimental subject in occupational exposures from the very beginning of activities which could be called an occupation. The recognition of the existence of toxic fumes and dusts associated with work in mines and smelters extends back many centuries. In each era, the monetary value of the man, at first in terms of replacement, largely determined to what extent the crude control measures were applied..." (39, p. 104)

This analysis is also important as an acknowledgement of the economic roots of the human experiment which, Sterner says, is "never ended." Establishment of exposure limits using data other than those derived from medical examination or surveillance of exposed workers was clearly a giant step away from the experiment, but not a complete repudiation either of the experiment or of its economic motivations. A 1967 editorial in the *Journal of Occupational Medicine* (40, p. 578) stresses the need for TLVs which "will not be unnecesarily restrictive." Stokinger comments that, while initial hazard evaluations of chemical compounds are being conducted by industry.

> "...plant industrial physicians and engineers are making observations on the workers and their work place environment. Some TLVs so derived have been based on a decade or two of industrial experience... . *Clearly, such procedures can yield indisputable data on which realistic TLVs can be derived*, unsurrounded by that uncertainty and doubt which requires incorporation of large safety factors, leading to wasteful overengineering of plant processes."

He returns to the theme of overprotection by claiming that TLVs

> "...provide safety without overprotecting the worker or overengineering plant processes, practices which private enterprise can afford only at the expense of the consumer public which pays the increased cost of their product." (33, pp 44, 45: emphasis in original; see also 41)

Some implications of this economic approach are explored in the later sections of this report dealing with the concept of acceptable risk and with the shift toward safe-person rather than safe-place strategies.

Sensitivity, quality and consistency

Whether human beings or test animals are being experimented on, an important consideration is the choice of tests. The tests carried out may, or may not, be the most sensitive ones for detecting adverse effects on human health. A further issue is the definition of an adverse health effect — an issue which has arisen in the setting of TLVs for a number of well-known toxic substances such as lead, and which is discussed separately in a later section of this report. Stokinger has noted that the designation of a threshold or no-effect level

> "...is intimately tied to the criteria used for its determination. Clearly, a 'no-effect' level based solely on no changes in body weight or organ weight to body weight ratios or in tissue morphology, might prove to be an 'effect level,' had more subtle and incisive variables such as changes in enzyme activity and intermediary metabolites, respiratory function and hematologic variables been studied in detail." (33, p. 41)

In the light of this observation, it is important that, for the most part (as of 1968), "rather simple and unsophisticated" criteria had been used to develop TLVs, according to Stokinger. Roughly half (201 out of 414) guarded against changes in a particular organ or organ system, and another 40 per cent (165 out of 414) were set on the basis of irritation. It should not be supposed that these criteria (especially in the irritation group) imply that the TLV corresponded to a no-effect level. In contrast, only eight TLVs had been established with reference to biochemical changes. Only six guarded against cancer, an especially striking omission whose motivations and implications are explored separately in a later section of the report. A further observation of importance is that, of the 550 TLVs set by 1973, only for three had there been any contribution from behavioral toxicology. Yet Herbert Stokinger wrote in 1974 that "[b]ehavioral toxicology...has been credited, at least by Soviet admission, for their lower, and in their eyes, more appropriate standards" (41).

We ultimately reach the value-laden question of the *relevance* of experimental data for the particular purposes of setting occupational exposure limits. More mundane is the issue of quality control. The author has located no systematic surveys of the quality of data underlying occupational exposure limits for workplace contaminants, although the need for improvements in the underlying information base is often acknowledged. This apparent lack of attention to quality control on the part of standard-setters is particularly significant in view of the revelations of the past several years concerning the grossly inadequate testing procedures used by IBT Laboratories, one of many commercial laboratories carrying out chemical testing under contract to manufacturers (42). Alan Lisook, of the U.S. Food and Drug Administration, has suggested that quality control problems in laboratory studies are widespread among laboratories conducting studies, for regulatory

Sensitivity, quality and consistency *continued*

purposes, for firms regulated by his agency (43). The history of the IBT case and the pattern of quality control problems described by Lisook only begin to suggest the overall dimensions of the quality issue as it affects toxicological testing. How far all this affects occupational health is not clear, so the present report can do no better than to cite two examples from today's *TLV Documentation* which suggest that the problem may be a serious one.

Acrylamide is assigned a TLV of 0.3 mg/cubic metre, based on calculations from a feeding study carried out on cats; it is "recommended that no more than 0.05 mg/kg/day be absorbed by workers. Assuming a respiratory exchange of 10 cubic metres/day, a TLV of 0.3 mg/cubic metre (0.1 ppm) may be calculated." The *Documentation* goes on to cite an unpublished communication (but no published studies) to the effect that "this limit has proven to be a practical working limit for the prevention of nervous disorder."

The feeding study itself (44, p. 180), conducted by Dow Chemical Co., involved one-year feeding of various dosages of acrylamide to cats and monkeys; it concluded that cats were more sensitive than monkeys, and that:

> "On the basis of gross observation for neurotoxic symptoms, 0.3 mg/kg/day of acrylamide was without any evidence of adverse effect in the cat after one full year of treatment. The dosage level of 1.0mg/kg/day of acrylamide caused only doubtfully significant effects. Higher dosage levels, i.e., 3 and 10 mg/kg/day resulted in definite neurotoxicity.
>
> From these results it can be safely assumed that the 'no effect' level of acrylamide for cats upon long-term feeding is probably 1.0 mg/kg/day, and certainly no lower than 0.3 mg/kg/day."

Quality control and experimental protocols in this study were unusual. Two of the three control cats died within the first month of the study, and the third was "sacrificed...after 171 days." having developed a severe case of mange. Two cats were started at each of the several dose levels: 10, 2, 1, 0.3, 0.1 and 0.03 mg/kg/day. Serious neurotoxic symptoms developed in both cats at 10mg/kg/day by day 53, at which point one cat was sacrificed and the other removed from exposure; by day 105, this second cat (which had been unable to stand at day 53) could stand and walk quite well.

Progressive but less severe neurotoxic symptoms were noted in the cats exposed to 3 mg/kg/day, both of which survived for the full year. One of the cats receiving 1 mg/kg/day was sacrificed at 152 days; the other showed intermittent neurotoxic symptoms starting at day 26 and continuing through the year.

Sensitivity, quality and consistency *continued*

At 0.3, 0.1 and 0.03 mg/kg/day, the picture becomes bizarre.

> "Two cats were started on each of these dosages. The animals on the 0.1 and 0.03 levels succumbed to spontaneous diseases before 102 days of the experiment had progressed without showing any neurologic effects. At the 0.3 mg/kg/day level, one cat was found dead in his cage after 106 days and the other survived for the full-year experimental period. Neither animal on the 0.3 mg/kg/day dosage showed any apparent effect upon gross observation which could be attributed to the ingestion of acrylamide."

No adverse effects on the brain or spinal cord of any test animal were noted on pathological examination. The positing of a no-effect level between 0.3 and 1.0 mg/kg/day for ingestion of acrylamide in the cat is based on observation of *two cats, one of which* (the survivor in the 1.0 mg/kg dose group) *clearly did exhibit symptoms of neurotoxicity* in an obviously ill-conducted and ill-controlled experiment. Intriguingly, Stokinger (45, p. 340) noted in 1956 (before any TLV had been set for acrylamide) that among its "toxicologically remarkable" characteristics were that:

> "A definite quantity of acrylamide will produce the characteristic central nervous system syndrome of disturbed gait, postural tremors, visual and auditory hallucinations and muscular atrophy, *irrespective of the dosage schedule used*" (Emphasis added)

and that:

> "There is an anamnestic response, in that following cure, lesser amounts of acrylamide recall the syndrome. Fortunately the effects are reversible, although in severe cases recovery may require years (in man)."

Although Stokinger's observations are referred to in the *Documentation*, there is no indication that these effects have been taken into account in determination of the TLV.

An issue not strictly of quality control, but closely related enough to be dealt with under this heading, is consistency in interpreting evidence of health effects. The case of hydrogen cyanide suggests that ACGIH's TLV committee has been seriously inconsistent in its treatment of human evidence. As noted earlier, the ceiling limit of 10 ppm for this substance is based on evidence of acute toxicity cited in *Schadliche Gase*, published in 1931. The documentation notes that the TLV committee voted down a proposed reduction in the ceiling value from 10 ppm to 3 ppm in 1979. This would have provided at least some margin against effects of habitual exposure like those reported by El Ghawabi *et al.* in 1975 (46).

Sensitivity, quality and consistency *continued*

In three factories this team found average breathing zone concentrations of hydrogen cyanide of respectively 10.4, 6.4 and 8.0 ppm; *no* measured concentrations in the second and third factories were above the 10 ppm ceiling. Yet workers in the plants showed a sharply elevated incidence of headache, weakness, changes in taste and smell, giddiness, throat irritation, vomiting, and difficulty in breathing produced by physical effort in exposed workers as compared with controls; and "mild to moderate" enlargement of the thyroid, without accompanying clinical symptoms, in more than half of the exposed workers. Two workers suffered from psychotic episodes (from which they recovered within 36 to 48 hours after removal from work) during the investigation in the factory with the highest exposure levels. Louch (1, p.5) has noted a similar failure on the part of ACGIH to acknowledge demonstrated health effects, and to set TLVs at a level which would provide a margin of safety, in the case of the TLV for sulphur dioxide.

The rejection of such evidence for purposes of determining permissible exposure limits raises serious questions in view of the general emphasis on human health effects as the ultimate validator of TLVs. These questions involve, if nothing else, the weighting of uncertainty in cases of disputes over scientific evidence. In this context, it is not clear how the "accumulated background and experience" (36) of the members of the TLV Committee is operating. Examples like that of hydrogen cyanide certainly lend weight to the comment of Husman (47, p. 31) that TLVs "are administrative recommendations, not health-based criteria."

If a single theme emerges from this chapter, it is the degree of *uncertainty* which has characterized the history of numerical exposure limits — uncertainty about the proper extrapolation to human subjects of results from animal experiments; uncertainty about the quality of the data underlying such extrapolations; and uncertainty about the extent to which the process of setting standards or limits has involved considerations of the sort typified by the perceived need to avoid what Stokinger called overprotection and overengineering. As argued in the chapter which follows, the enterprise of setting occupational exposure limits has embodied a "quest for certainty". In the course of this quest, it has often been the case that scant attention has been paid to the uncertainties outlined in this chapter, as well as to others which may be still more fundamental.

TLVs: the quest for certainty

The legacy of Paracelsus

Marcus Key of NIOSH wrote in 1972 about occupational exposure limits that "the concept on which they are based is simple — that a toxic substance can be reduced to such a low concentration that it has no effect on health" (48, p. 707). This concept, traceable directly to Paracelsus' famous observation about the relation

The legacy of Paracelsus *continued*

between dose and poisoning, is very often invoked in discussions of the rationale for exposure limits. Smyth wrote in 1954 that:

> "Any substance can be tolerated in some particular daily intake, with the possible exception of beryllium, the action of which is not yet fully understood." (49, p. 203.)

In 1968, Hatch suggested that "the whole foundation of industrial hygiene and the very basis upon which many industries depend for survival" would be threatened by a serious challenge to

> "...two basic characteristics of the inherently poisonous chemicals and potentially dangerous physical stresses which workmen may encounter in one or another industry or occupation: 1) there exists a systematic dose-response relationship between the magnitude of exposure to the hazardous agent and the degree of response in the exposed individual, and, 2) there is a graded decrease in the risk of injury as the level of exposure goes down, which risk becomes negligible when exposure falls below a certain tolerable level." (50, p. 1)

But "tolerable" effects or negligible risks are not the same as absent effects or zero risk. Determination of the dose or concentration below which effects (or intolerable effects) are not observed in turn rests on at least two distinct factors: the *definition* of tolerable effects or non-negligible risks, and the *sensitivity* of the analytical system used to assess such effects. Experiments designed to assess the lethality of acute exposures to a particular chemicals are generally much less sensitive, in that they will detect ill effects only at much higher exposure levels, than will experiments designed to measure effects of chronic exposures. And some organ systems are much more vulnerable than others to the effects of particular types of chemicals; the choice of which systems to examine, and the sophistication of techniques of examination, will affect the sensitivity of the test.

Science and judgement

A considerable degree of sophistication about the nature and limitations of occupational exposure limits (or, to be more accurate, permissible concentrations) is evident in wartime and early postwar North-American discussions of standard-setting. Sterner, in 1943, highlighted the practical problem of "defining what is 'harmful'" for standard-setting purposes, noting the existence of controversy over exposure levels at which "the injuries sustained are slight and quickly reversible, or amount only to a discomfort — tolerable, but unpleasant." (51, p. 514). The preamble provided by Cook to his 1945 compilation of "Maximum Allowable Concentrations of Industrial Atmospheric Contaminants" from several sources warns against assuming "that compliance with the figures listed

Science and judgement *continued*

would guarantee protection against ill health" (3, p. 937). Schrenk, in 1947, noted the existence of "definite disagreement regarding the interpretation" of the concept of lack of injury or occupational disease (29, p. 55).

Yant, in 1949, struck a note of caution by criticizing the inference of "precise quantitation and association of environment with toxic manifestations" which could be drawn as a result of terms such as "maximum allowable (or permissible) concentration." Arguing for "dissociating the idea of maximum tolerable stress from the concept of hygienic standards," he pointed out that "[n]o engineer would think of using the near failure limits of materials for designing a structure." Yant acknowledged a distinction between criteria of comfort, based on "sensory effects of transient and, *on the basis of present knowledge, harmless* manifestations such as slight irritation of the eyes or nose, nauseating odors, and mild degrees of narcotic effects..." (52, pp 9-10). A similar approach was taken by Elkins (53), who noted that some people argued that effects like lachrymation due to formaldehyde, headache from absorption of nitroglycerin, and metal fume fever from inhaling zinc fumes, should be ignored for purposes of setting permissible limits. (Elkins, to his credit, appears to have rejected this argument.)

TWA becomes an institution

Experiments to assess the effects on animals (and, indeed, on human volunteers) of repeated or continuing exposure to hazardous substances have frequently used an eight-hour period of exposure, on the basis that this corresponds at least roughly to the pattern of exposure which would be experienced by an industrial worker, at a roughly constant concentration. Henschler (54) has suggested that this may be one of the factors responsible for the statement of human exposure limits as time-weighted averages. An alternative explanation is suggested by what appears to be the first use of time-weighted averages as indicators of human exposure. Bloomfield (55), writing in 1933, multiplied the amount of time spent by workers in several activities, which entailed dust exposures which differed by three orders of magnitude, by the concentrations of dust observed in the vicinity of each activity as a way of calculating workers' "true average exposure" to dust.

However, the step from assessing exposure during an eight-hour day to stating maximum permissible exposures in terms of an *average*, rather than maximum concentration is not a self-evident or self-explanatory one. Atherley (35) has produced a detailed critique of the concept of a time-weighted average as used in occupational exposure limits, showing that its conceptual bases (the failure to distinguish between exposure and dose, and the associated assumption that for the range of values which are of concern in the occupational environment dose can be equated with

TWA becomes an institution *continued*

the product of concentration and time) have not been scientifically validated, and indeed that serious efforts to do so have only been undertaken very recently.

The arguments made in that article will not be repeated here. In view of these factors, however, the lack of explicit justification in the literature for the principle of TWA and for the 8-hour base is striking. Indeed, the trend among North American industrial hygienists since the end of World War II appears to have been one of a steadily *declining* concern with the uncertainty surrounding this set of assumptions. The warnings of Yant in 1948 (52) and the Committee on Chemical Agents of the Panel on Environmental Hygiene at a 1950 Congress on Industrial Health (56) appear to have had little influence on the acceptance of time-weighted average. Adams *et al.* warned in a paper first read in 1950 that:

> "The time-weighted average may be applied universally in evaluating repeated exposures only if two conditions are met: (a) that the numerical values of CT (concentration x time) are directly proportional to severity of toxic effect for all possible values of C and T (CT = K) and (b) that the toxic effect or 'value' of any one component of a day's exposure...is the same regardless of its chronological relationship to other components. ...Actually, it is known that CT does not correctly portray the toxicity 'value' of exposures, although the numerical results may be nearly constant in some instances and over limited ranges. There appears to be no information whatever bearing upon the second condition. Accordingly, it must be concluded that at present there is no scientific basis for the use of the time-weighted average to integrate varying exposures." (57, p. 65)

Yet in 1953, when an explanatory preamble was first added to the ACGIH list of TLVs, it indicated without further explanation that the values cited were intended as averages over an eight-hour working day. According to Stokinger,

> "This definition of the TLVs is important to note, because it differed from the general understanding of industrial hygienists of the original term, MACs or maximum allowable concentrations, which are essentially ceiling values below which all values must fluctuate. ..."
>
> ...Gradually the definition appearing annually in the preface to the TLVs became firmly established and is now accepted generally." (58, p. 9)

In 1955, Stokinger noted, again without further explanation, that "the concept of the limit is that the summation of physiological effects of such exposures shall not be greater than the effect of exposure to a constant concentration at the level of the limit" (59, p. 176). In 1961, in discussing the equation of dose with the

TWA becomes an institution *continued*

product of concentration and time in setting permissible limits. Stokinger did not feel it necessary to defend the assumption beyond a reference to it as a "sound toxicological principle" (60, p. 116).

It is interesting to contrast the embrace of the TWA concept in North America with the reluctance to accept it in the Soviet Union. In 1972, Sanockij (61, p. 14) noted that Soviet values for Maximum Allowable Concentrations (MAC) related to "the maximum concentration that must not be exceeded during the shift" and went on to argue:

> "Those who support the need for averaging the concentrations usually argue that the biological effect is determined by the dose of the poison that enters the body. Fluctuations in the concentration of poisons of cumulative type, according to these authors, are thus of no importance, since they are smoothed out within the organism. However, this contradicts the evidence that more severe lesions result from the intermittent actions of pathogenic environmental factors than from their continuous, uniform action."

He went on to argue that as sampling techniques improved in their ability to provide reliable information about peak concentrations on a short-term basis, the use of TWA would become less, rather than more defensible.

If time-weighted averages were rapidly accepted, concern about their misuse or too-literal interpretation remained. Irish (38), in 1965, warned of this danger and supported a system of multiple boundaries or standards involving both time-weighted averages and maximum (ceiling) limits. The Dow Chemical research team of Adams *et al.*, quoted earlier (of which Irish was a member), in 1952 tried to resolve the conflict between the need for some sort of industrial hygiene standard and the inadequacy of the concept of time-weighted average in the following manner:

> "When air samples are taken intermittently over relatively short intervals of time (5 to 30 minutes) in representative work locations throughout the whole workday, the concept of the [industrial hygiene] standard may be defined as that concentration below which practically all analytical results must fall.
>
> ...[A] value of 25 ppm is suggested for carbon tetrachloride. The extent to which vapor concentrations must fall below 25 ppm may be indicated by the specification that the average of all analytical values should not exceed 10 ppm." (57, p. 57).

TWA becomes an institution *continued*

ACGIH subsequently made several efforts to accommodate those who have expressed concern about the limitations of the TWA concept. These efforts have taken three forms:

Ceiling values: starting in 1963, ACGIH began accompanying certain TLVs with a "C" (for ceiling) notation, meaning that the concentration specified was one which, in their opinion, should not be exceeded even instantaneously.

Short-term limits: In addition to ceiling limits, ACGIH for a while referred users of the TLV list to a list of Short-Term Limits (STLs) published in 1968 by the Pennsylvania Department of Health which represented the maximum concentration to which a worker should be exposed for the time specified (which could be 5, 15 or 30 minutes), provided as well that the 8-hour TWA was not exceeded and that sufficient time elapsed for recovery between exposures (62). Subsequently, ACGIH promulgated its own short-term exposure limits (STELs), based in part on the Pennsylvania limits and stated on a tentative basis in its 1980 list of TLVs (63), based on a 15-minute time-weighted average exposure, for a number of substances.

The same factors were taken into account in the setting of ceiling values and STELs — in general, whether or not "excursions of concentration above a proposed limit for period up to 15 minutes may result in (a) intolerable irritation, (b) chronic, or irreversible tissue change, or (c) narcosis of sufficient degree to increase accident proneness, impair self-rescue or materially reduce work efficiency" (62, p. 49).

Excursion factors represented an attempt to specify the extent to which a time-weighted average concentration could be exceeded, based upon "a number of factors such as the nature of the contaminant, whether very high concentrations — even for short periods — produce acute poisoning, whether the effects are cumulative, the frequency with which high concentrations occur, and the duration of such periods" (62, p. 39). At least two bases for calculating permissible excursions for those substances not covered by short-term or ceiling values have been suggested. One linked the excursion factor to the eight-hour time-weighted average, according to the table reproduced below.

TLV (8-hour TWA)	**Excursion Factor**
TLV: 0-1 (ppm or mg/cu. metre)	3
TLV: 1-10 "	2
TLV: 10-100 "	1.5
TLV: 100-1000 "	1.25

TWA becomes an institution *continued*

In other words, the maximum permissible concentration for substance with an 8-hour TWA of 5 ppm would be 10 ppm (5 x 2); for a substance with an 8-hour TWA of 50 ppm, 75 ppm (50 x 1.5).

According to ACGIH:

> "While no rigorous rationale was provided for these particular values, the basic concept was intuitive: in a well controlled process exposure, excursions should be held within some reasonable limits. Unfortunately, neither toxicology nor collective industrial hygiene experience provide a solid basis for quantifying what those limits should be."(64, p. 5)

ACGIH therefore proposed in the 1983-84 TLV list to replace the excursion factor approach with one based on a belief that "the maximum recommended excursion should be related to the value generally observed in actual industrial processes." Based on surveys of the general distribution of exposure values observed in industrial hygiene surveys conducted by NIOSH, the new excursion limit recommendation was:

> "Short-term exposures should exceed three times the TLV-TWA for no more than a total of 30 minutes during a work day and under no circumstances should they exceed five times the TLV, provided that the TLV-TWA is not exceeded..."

Henschler (54) has criticized both the use of ceiling limits and the ACGIH's table of excursion factors as "unsatisfactory from a scientific point of view" — the latter because it "does not take into account well established rules of the dose-response relationship," and the former because it "lacks substantiated toxicological criteria and does not comply with the basic requirements of chemical-analytical air monitoring." Henschler's comment on ceiling limits is an indication of the extent to which operational considerations have come to dominate the process of standard-setting for the work environment. His criticism of the excursion factor concept is, if anything, too mild in that it does not capture the largely arbitrary nature of the proposed excursion factors. Yet the technique which ACGIH substituted for excursion factors is bizarre, judged by the history of the development of occupational limits. It relies on what is essentially an engineering judgement about how a "well controlled" process ought to operate — a striking contrast with Elkins' remarks in 1948 about the weakness on relying on engineering controls without assessing workplace exposures on the basis of permissible exposure limits (53).

Authority in numbers?

The responses to the limitations of TWA documented in the preceding pages come close to suggesting the existence of a numbers-at-any-cost approach on the part of ACGIH, at least. So, too, did the 1961 comment of Stokinger (60) to the effect that the lack of detail and documentation provided in the ACGIH TLV list was an asset rather than a liability: "[I]t was the [TLV] Committee's opinion that in a list of this sort there is great value in simplicity — a substance, a number; memory for the important item is obscured by detail."

The preoccupation with numbers and the decline in concern for the uncertainties surrounding the concept of dose used in calculating TWAs are probably a reflection of the undeniable usefulness of numerical exposure limits, in whatever form. This usefulness had become apparent long before their incorporation into U.S. federal legislation at the beginning of the last decade. Elkins, in 1948, saw the use of permissible limits as an alternative not only to reliance on improved engineering controls without any immediate test of effectiveness, but also to *ad hoc* reliance on periodic medical examinations which might well fail to detect serious, ultimately fatal occupational hazards. He characterized this latter option as a return to "the dark ages of empiricism in occupational disease control" (53, p. 24).

By 1950, the Committee on Chemical Agents, whose warnings about the scientific limitations of time-weighted averages were cited earlier, had also noted the widespread use of permissible limits as a way of evaluating the exposure of workers to hazardous substances (56). In 1954, Smyth (49) commented that:

> "The industrial hygienist feels insecure when a plant which concerns him is using a chemical until he has an authoritative statement of [a permissible limit]. When he has obtained such a statement his insecurity tends to approach zero."

In a 1956 symposium on threshold limits Miriam Sachs, a staff member of a state Department of Health, noted that:

> "[T]hreshold limits satisfy the need for a tool essential to the protection of the health of the worker. The quantity of technical information concerning the biological action of old and new chemicals is so vast that no single practitioner of industrial hygiene can be expected to be able to assimilate more than a very small fraction of this mass of material."

Sachs went on to quote a personal communication from F.W. Church of Esso Research and Engineering Company to the effect that:

Authority in numbers? *continued*

> "Almost 100% confidence can be placed in the threshold limits where they are being used for evaluating and controlling of an industrial environment. This is particularly true in the use of these limits as a base line for calculating control design specifications... ." (65, p. 275)

She also cited results of a questionnaire survey of the U.S.-based members of the American Industrial Hygiene Association (AIHA) and ACGIH: of the 326 completed questionnaires (of 1050 circulated), 53 respondents expressed "100 percent" confidence in the TLVs; 173, "80 percent" confidence. All but three of the respondents agreed with the need for TLVs, although there were numerous requests for more extensive documentation.

In a paper delivered at the same 1956 symposium, Smyth (66, p. 279) noted that, in addition to the needs of regulatory agencies and industrial hygienists in the private sector, TLVs also met the needs of the "arm-chair industrial hygienist" who

> "...uses threshold limits to advise upon the selection of a chemical for a particular application, to select a suitable application for a little known chemical and to bolster sales arguments for a chemical or mixture of chemicals.
>
> When the industrial hygienist is asked to advise whether acetone, propyl acetate, methylene chloride would be the safest solvent in a particular application, it may be believed that his answer is based on a profound knowledge of toxicology, but actually he recalls the threshold limits, or refreshes his memory by consulting the list while the questioner waits on the telephone. Then the answer is given *as if the list recorded comparative toxicities*, perhaps adding a bit of qualitative information on fire hazard and the type of injury from an excess." (Emphasis added)

A hygienist from the Bethlehem Steel Corp. pointed out that permissible limits reduce the "insecurity" of hygienists by providing "a *scientific* basis for consideration" of alternative control strategies. He used the example of a degreasing operation using carbon tetrachloride as a solvent: despite local exhaust ventilation, concentrations near the tank are on the order of 250 ppm. In the absence of permissible limits, a cautious approach would involve *both* substituting a safer solvent and redesigning the exhaust system with 100 per cent capture as a goal. This approach would obviously be quite costly.

As an alternative, he suggested substituting trichloroethylene or perchloroethylene, which are both less volatile than carbon tetrachloride, thus reducing solvent losses.

Authority in numbers?
continued

> "The threshold limit for trichloroethylene and for perchloroethylene is 200 ppm and the vapor concentration was found to be on the order of 250 ppm when carbon tetrachloride was used. Because of the lower vapor pressure of the proposed substitutes, the amount of vapor getting into the room air will be much less and the exposure of the workers will be reduced to a value well below 200 ppm." (67, p. 288)

The quoted recommendations constitute a use of numerical exposure limits not previously mentioned in this report: as a basis for recommending substitution of less for more hazardous substances — in other words, as the basis for evaluations of comparative hazard. Although the quotation dates from 1956, it is by no means the first such recommendation in the literature. A recommendation for the use of less volatile substitutes for benzene, which also were believed less toxic to the blood and nervous system, was one of the conspicuous conclusions of the National Safety Council study of benzene poisoning in the late 1920s (21, p. 74). And Sterner noted in 1943 that numerical exposure limits allow "a more accurate use of engineering methods, by indicating the requirements which must be met by devices for ventilating, inclosing or otherwise controlling the hazardous materials" and facilitate "a more accurate governmental inspection and regulation of the exposure." (51, p. 517) What was (relatively) new was the ACGIH stamp of approval, and the convenience of a list of values which could be used for design and engineering purposes.

Validating the scientific underpinnings of occupational limits may have seemed relatively unimportant — particularly if it might result in greater uncertainty of precisely the type TLVs were viewed as largely having eliminated. In 1947, Schrenk would warn, with respect to tables of permissible concentrations, that "not enough attention has been given to their limitations and how to use them intelligently. There is a tendency to place too much reliance on figures, with little or no consideration of their real meaning" (29, p. 55). By contrast, consider the practical outlook of hygienists like Elkins, who the following year defended permissible limits even based on rough comparisons with the toxicity of other, more familiar substances ("taking a value out of thin air") where the alternatives were no controls; controls based solely on good engineering practices; medical examinations; and control based on a tentative permissible limit (53, p. 24).

To engage in a bit of further speculation, consider the role of the industrial hygienest. Smyth observed in 1956 that "it is a minority of the profession of industrial hygiene who have regulatory responsibilities. Most of our colleagues act through obtaining voluntary cooperation with their judgements." Whether working for industry, as did a great many hygienists, or for government,

Authority in numbers? *continued*

they occupied and occupy a sort of boundary zone, analogous to that occupied by company doctors (68). Both are faced with conflicts between professional norms (the protection of health) and their organizations' priorities, whether they report to an industrial management concerned with maximizing returns and minimizing costs, or to a government agency which must limit the extent to which it engages in overt conflict with the private sector. These problems, occurring in a pre-OSHA political environment, may have been especially severe for hygienists working within industry.

Smyth pleaded in 1956 for improved documentation (which another article of his (92), published in the same year proceeded to provide) for ACGIH permissible limits, to demonstrate to industry that they did not represent "arbitrary decisions having no regard for the realities of competitive industrial existence." Thus, a major function of permissible exposure limits was to increase the "clout" of the hygienist in dealing with industrial clients or employers. But if the authoritativeness of the values (and the hygienist) would have been increased by expanded documentation, it might have been *diminished* by acknowledgement of the controversial or dynamic nature of some of the underlying scientific assumptions.

It is arguably this set of considerations which explains an apparent internal contradiction in the approach of ACGIH, and of industrial hygienists, to the use of occupational limits. On the one hand, a recurrent theme in discussions of TLVs has been the need for interetation by a properly skilled and trained individual: "We will never devise standards that can be safely used by the Knob Twirler" (38, p. 549). On the other hand, the quest for numerical (that is, at least superficially non-judgemental) values has been pursued almost obsessively, to the point where on detailed examination they emerge as having become divorced from any scientific underpinnings.

Particularly during the earlier years of the development of TLVs, those involved with their development readily conceded the incompleteness of the data and the need for further testing and refinement of values assigned as TLVs. In 1943, Sterner commented that a few of the permissible exposure limits then available were

> "...based upon a considerable amount of careful clinical evidence, but many are very tentative in character, and are meant as nothing more than the best estimate as to a safe level." (51, p. 517)

"[W]e emphasize paucity of our present information, not the failure of the principle," wrote Sterner in 1955 (20, p. 28). And a year later he was to note that:

Authority in numbers? *continued*

> "[E]ven though rigid standards were described which would satisfy a discriminating jury of scientists, the available data for establishing threshold limits for all but a very few substances would fail to satisfy such limits. The real use for threshold limits, as a guide for industry in the control of exposures and as a measure from action by governmental agencies, demands a continuing improvement in the quality and quantity of the methods by which truly valid criteria may be achieved."

But refinement of data, of the type which has led in incremental fashion to the reductions of TLVs for many substances, does not add the element of uncertainty that would be introduced by reassessing much of the conceptual basis for setting of permissible limits. Uncertainty might have the effect of undermining the authority and perceived professionalism of the users of TLVs, in government and in industry, in a situation where — given that permissible exposure limits were being used as a basis for engineering controls — virtually any values which were persuasive, however imperfect, were clearly seen as being better than none.

If the search for a firm scientific base appears largely to have been abandoned with respect to the setting of permissible limits for concentrations of hazardous substances in the work environment, it has not been abandoned altogether. Instead, the scientific focus has shifted to the development of more precise methods of measuring the levels and impacts of hazardous materials in the body of the individual worker. The history and possible motivations of this shift are discussed in the final section of this report, since they clearly represent the current thrust of medical/scientific/technocratic endeavor in the field of workplace health.

Effects of combined exposure

Further evidence of ACGIH's quest for numerical simplicity is its treatment of simultaneous (or successive) exposure to a number of substances. The general assumption is that effects are additive "in the absence of information to the contrary." An exception is made in cases where the effects are known (believed?) to be independent: examples used by ACGIH in the 1983-84 TLV listing (64) include simultaneous exposure to hydrogen cyanide and sulphur dioxide, or to lead and sulphuric acid.

This assumption of the additive nature of toxic effects would be extremely difficult to justify on an empirical basis, because of the multiplicity of potential combinations. Further, it is impossible to *dis*prove, because any number of discovered instances of multiplicative or synergistic effects can be dismissed as exceptions to a general rule!

Effects of combined exposure *continued*

Yet the literature contains very few admissions of the uncertainties surrounding the effects of combined exposures. Ball, in 1959, noted the impossibility of examining more than an insignificant fraction of all possible mixtures experimentally, and suggested a preliminary theoretical framework, based on Selye's analysis of the impact of combined stressors, as "a starting point for the prediction of the physiological action of multiple poisons" (69). And Hatch pointed out in 1972 that:

> "[T]hese interactions are not well understood. ...[S]imultaneous exposure to two toxic agents having basically different mechanisms and sites of action may present highly complex situations for which the simple application of their separate permissible limits will not necessarily give adequate protection." (70, p. 157)

Recent evidence suggests that even when workers are exposed to airborne contaminants whose mechanisms of toxicity are similar, ACGIH's approach does not provide an adequate basis for assessing toxic effects. Studies of Finnish and Swedish spray painters exposed to combinations of organic solvents which would be considered "acceptable" on the basis of calculations using the ACGIH additive formula (47, 71). In the Swedish study, the (Swedish) permissible exposure limits for individual substances used in this calculation were in many instances considerably lower than the 1983-84 ACGIH values. These studies raise two distinct issues, but they do not provide a basis for distinguishing between the two in the specific context of the study. One is the validity of the assumption that effects of combined exposures are additive. The other is the adequacy of permissible exposure limits for individual substances, in terms of whatever criteria are being used as the basis for determining permissible exposures. Another suggestive example of the kind of combined effects which may not be taken into account in the determination of permissible exposures is the striking increase observed in the carcinogenic effects of benz(a)pyrene when it enters the lungs of laboratory animals attached to fine particles of ferric oxide (72, 73).

One of the most reflective recent looks at the nature of standard-setting was provided by Henschler (32) in 1984. He acknowledged that current approaches to setting exposure limits are based on a series of compromises, of which the treatment of mixed exposures is one. According to Henschler, the conditions for the application of the additive approach "are never fulfilled":

> "Many occupational toxicants pass through the organism concurrently and yet act independently from each other. There are, however, exceptions with spectacular magnification of the activity of one component or the other or of both in the case of interactions at the target tissue or at the sites of biotransformation. Dramatic increase of toxicity may result

Effects of combined exposure *continued*

if a normally very potent pathway of detoxication is blocked by otherwise ineffective concentrations of a concomitant toxicant... The likelihood prevails that this type of disastrous interaction will be disclosed by systematic studies of the mechanisms of action, rather than by chance. Considering this, one can only recommend that case by case evaluations of mixed exposures be performed by the best scientific expertise. This compromise will certainly not be favoured by regulatory agencies, but it will foster relevant scientific work to build the foundations for a more satisfactory escape from a real dilemma."

Health, risk and acceptability

Introduction

It was noted at the start of the preceding chapter that the conceptual basis of permissible limits can be traced directly to Paracelsus' famous observation about the relation between dose and poisonous effect. As an indication of the extent of this influence, Herbert Stokinger, then-Chairman of the ACGIH Threshold Limits Committee, wrote in 1964 that TLVs

> "...are based on the premise that, although all chemical substances are toxic at some concentration experienced for a period of time, a concentration exists for all substances from which no injurious effect will result no matter how often the exposure is repeated." (74, p.591)

Intriguingly, Stokinger went on to concede that setting thresholds for certain categories of substances, such as chemical free radicals or free-radical formers, "is erroneous in the sense that *the degree of risk associated with the limit is not stated*." (Id., emphasis added).

This admission suggests that thresholds may have an important social function, quite apart from (and perhaps even coming into conflict with) the scientific basis for setting permissible exposure limits. To put the matter another way, the concept of thresholds may be defensible (as argued later in this chapter) only on the basis of thoroughly non-scientific judgements about what does, and does not, constitute an adverse effect.

Green (75), in a perceptive recent article, attributes to "those at the commanding heights" of the industral hygiene profession the recognition

> "...that the great importance of the threshold concept lies in its ability to *naturalize* the social relations of toxic exposure. It allows industrial hygienists and occupational physicians to argue that exposure levels in the workplace are not merely the best that the company can afford, but that these exposure levels are biologically safe — they are below the threshold of effect."

Introduction *continued*

Weight is lent to this interpretation by Hatch's 1970 warning that:

> "One of the most important principles upon which occupational health programs are based is that exposure to a toxic agent may be permitted up to some limit of tolerance above zero, within which man can cope successfully with the insult with no significant threat to his health. It is only on the demonstrated reality of this concept that the establishment and continued operation of a great segment of modern industry can be justified... . Any challenge to this operating principle must, *therefore*, be met with the utmost vigor by those responsible for industrial health maintenance... ." (76, p. 687: emphasis added).

Also apposite is Zapp's 1977 comment on the threshold concept, to the effect that

> "...if there is no such thing as a no-effect but finite level of exposure, then the TLVs must be considered in terms of that which is socially and politically acceptable, rather than in terms of what is scientifically correct." (77, p. 425)

It is hard to deny that the concept of a threshold enables industrial hygienists to make an argument from the "scientific correctness" of the values proposed which is at least superficially credible. As is argued later in this section of the report, and as is suggested by examples from the TLV Documentation, the ACGIH TLV-setters have often not done this in practice. Instead, they have relied (as they must) on other bases for standard-setting. Though industry, and industrial values, have been involved in the determination of TLVs, it is rather more difficult to substantiate the charge that an approach to setting permissible exposure limits based on the concept of thresholds has been chosen and defended for the reasons suggested by Green. It may well have had the effect he suggests, but the two conclusions are not quite the same.

The need to define health

Stokinger wrote in 1955 (59) that TLVs were designed to prevent "harm to (the worker's) physical or mental well being." Other early post-World-War II discussions of permissible exposure limits ndicated that such limits were not in any sense (nor were they intended to represent) no-effect levels, and could only be understood in terms of a particular definition of health and (therefore) of harm to well-being.

Elkins, in 1949, noted that the establishment of Maximum Allowable Concentrations (as they were then widely called) involved a choice of a particular point on the bottom end of a dose-response curve; suggested that "if the illness is rather minor and transient, the MAC can be chosen at a level which does affect

The need to define health *continued*

a minority of workers, but (which) should be below the value where the average individual suffers"; and noted the existence of a point of view holding that so-called minor effects should be ignored in the establishment of MACs (53, p. 23).

The Committee on Chemical Agents which reported to the Ninth Annual Congress of Industrial Health in 1950 was chaired by Henry Smyth and included many, if not all, of the most influential figures in the development of exposure limits in postwar America: Warren Cook, Philip Drinker, William Frederick, Donald Irish, and Herbert Stokinger. Cook was the compiler of the list of suggested permissible limits (3) published in 1945 which the ACGIH "adopted as its own" (4); Drinker, of the Harvard School of Public Health, one of the authors of Massachusetts' prewar list of maximum acceptable concentrations of toxic gases (78); Fredrick, the Chairman of the ACGIH TLV Committee in 1950; and Stokinger, the holder of that position from 1962 to 1975. The Committee noted that four different concepts of the level best suited to hygenic control had been used in the setting of permissible exposure limits:

"(a) Plus or minus: the maximal time-weighted average concentration which produces only minor injury, and that in a very small proportion of exposed workmen.

(b) Safe: the maximal time-weighted average concentration which sound evidence leads one to believe will cause no demonstrable illness or other symptoms of toxic effect in any workman during a lifetime of industrial exposure.

(c) Bench mark: A concentration based on the belief that any unnecessary exposure is undesirable—a concentration lower than that of "a" or "b", one as low as is consistent with practical engineering control.

(d) Comfort: A concentration lower than that of 'a' or 'b', and representing the maximum which in a short time is not objectionable to 9 out of 10 of a group of persons not accustomed to inhalation of the substance." (56, p. 605)

These four concepts were cited by Smyth in 1956 in his compilation and documentation of the ACGIH TLVs — the first such compilation of the evidence underlying the values to be published since Cook's 1945 article. The Committee found all four concepts "consistent with the goals of industrial hygiene." Yet they clearly embody *distinct* criteria, some more restrictive than others, for judging the acceptability of effect. These criteria may, in turn, be underlain either by competing definitions of health and of ill effect, or by differing judgments about the acceptability of an effect whose detrimental nature is agreed upon.

The first explicit recognition in the North American literature of differing definitions of adverse effect as they relate to comparisons of exposure limits among jurisdictions appears to be Elkins' 1961

The need to define health *continued*

analysis of "Maximum Acceptable Concentrations: A Comparison in Russia and the United States" (79). He noted that Soviet exposure limits for hydrocarbon and chlorinated hydrocarbon solvents were drastically lower than those in the United States (the ACGIH values) by factors ranging from two (for turpentine) to 42 (for vinyl chloride and chloroprene). Other values were less divergent, with a few exceptions like chlordane and lead (where the Russian values were one-twentieth of the American), acrylonitrile (where the Russian value was one-fortieth of the American) and metallic mercury, Lindane, and Tellurium (for which Russian values were one-tenth of the American).

Elkins explained the lower Soviet values, especially those for organic solvents, by the much greater sensitivity of the tests used on laboratory animals to measure toxic effects. He did not explore competing definitions of health or of adverse effects. Use of a more sensitive test system to detect chemical effects amounts, other things (for example, safety factors) being equal, to embodying a more restrictive definition of health — that is, one which tolerates fewer and less readily observable effects — in the scientific ideas which form the basis of permissible limits.

In 1960, A.A. Letavet (head of Moscow's Institute of Industrial Hygiene and Occupational Diseases) noted (80) that:

> "The term 'maximum allowable concentration' is understood in the Soviet Union as one denoting such concentrations of various chemical substances in the form of gases, vapors, and dusts in industrial atmospheres and possessing a toxic action which, by their constant effect on workers during the working day over a long period of time, can produce no pathologic changes or diseases detectable by means of modern examining methods."

He did not point out the obvious contrast with approaches such as that of the Committee on Chemical Agents or other US bodies.

In 1963 an Industrial Toxicology Delegation from the United States (whose members included Herbert Stokinger and Henry Smyth) conducted a four-week exploratory visit to the USSR. Their report (81) notes that the basic philosophical tenets of Soviet occupational hygiene standards included the setting of maximum allowable concentrations (not time-weighted averages) representing concentrations which "will not result in any deviation in the normal state of the organism as well as not result in disease"; the exclusion of technical feasibility considerations from the setting of MACs; and the pursuit of zero concentration as an optimum goal, regardless of the MAC. Asked the report by the Americans:

> "[W]hat is meant by 'any deviation from normal'? Is physiologic response to any type of stress to be equated with

The need to define health *continued*

injury produced in response to stress? In our discussions with many scientists, it became clear that any change in response to stimulus was considered a deviation from 'normal'. ...The concept implies that any concentration, however small, places an undesirable toxic or nuisance stress on the population. ...American standards for chemical exposures...are based on the premise that although all chemical substances are toxic at some concentration experienced for a period of time, a concentration exists for all substances from which no injurious effect will result, no matter how long the exposure."

It is also noteworthy that toxicological testing of new chemicals to be used in amounts greater than one or two kilograms was required before their introduction into industry was allowed. Two decades later, such pre-testing schemes are in the implementation phase in the United States and Western Europe. In Canada, authority to require pre-testing under certain conditions is conferred on regulatory authorities at the federal level (under the *Environmental Contaminants Act)* and in at least one province (Ontario) under the province's *Occupational Health and Safety Act.* This authority has never been used in the former case; neither, to the author's knowledge) has it been used by the Ontario government. Although the issue has only achieved political prominence in North America and Western Europe within the last decade, the need for premarket testing was observed in North America more than half a century ago by Alice Hamilton (7, p. 587), who observed in 1929 that:

"We are introducing new chemicals into industry all the time, chiefly as solvents; and everyone who knows anything about poisons is besieged by anxious manufacturers who do not want to use a new substance which may prove to be dangerous. More often than not we can give them no positive answer, and this usually means that the new chemical will be introduced cautiously and tried out, that is: the workers will serve as experimental laboratory animals, and everyone will hope that the danger, if there is any, will be discovered before it has had time to do much harm."

And the Soviets had banned or drastically restricted the use of pesticides including dieldrin, endrin and parathion whose use was only to be curtailed in the United States a decade later. The manufacture of a few specific chemicals had also been completely banned because of their carcinogenic effects.

The American visitors to the Soviet Union concluded

"...that the chief explanation for the differences in threshold limit values...lies in the philosophic approach to those limits and not in a difference in the sensitivity of methods used to establish those limits. Were the Soviet limits rigidly enforced,

The need to define health *continued*

the economic costs involved would probably result in a re-evaluation of the validity of the concepts underlying their limits."

This analysis was echoed in 1972 by Hatch (32, p. 135), who argued that the disparity in permissible limits

> "...arises out of basic differences in the definition of a state of health and from conflicting views concerning the degree to which the defence mechanisms, which are a normal part of man's physiological endowment, can be safely drawn upon to offset any result from the offending agent."

In the same year I.V. Sanockij (61, p. 13), of Moscow's Institute of Industrial Hygiene and Occupational Diseases, contrasted the Soviet definition of MACs with the definition of TLVs relative to

> "...the conditions to which 'nearly all workers can be repeatedly exposed, day after day, without adverse effect. Because of the wide variation in individual susceptibility a small percentage of workers may experience discomfort from some substances at concentrations at or below the 'threshold limit': a smaller percentage may be affected more seriously by aggravation of a pre-existing condition or by development of an occupational disease'."

He went on to criticize the American definition for deliberately accepting "unfavorable effects and even occupational diseases in individual workers" — a criticism echoed by Roschin and Timofeevskaya (83) in 1975.

Intriguingly, however, Sanockij later in his paper (pp 14-16) supported a new definition of MAC which is in many respects strikingly reflective of the Western approach, referring to concentrations which will not cause the development of diseases or changes in the state of health "that go beyond the limits of adaptive physiological responses." And he went on to discuss the concept of threshold of harmful action, again as concentrations which "give rise to changes...going beyond the limits of physiological adaptive responses." Leaving aside for the moment the question of the sensitivity of test systems, a cynic might conclude that the confrontation between purism and economics predicted by the American delegation in 1963 had come to pass, making the Western approach more attractive. This view would be reinforced by Sanockij's statement of the task of the experimental hygienist, with respect to the long-term effects of small amounts of chemicals, as being

> "...to quantify the effect of an inadequate stimulus, to seek the thresholds of its action in order to obtain a basis for prophylactic measures";

The need to define health *continued*

by the rejection as "unrealistic" of the prohibition of all mutagenic chemicals; and by the acceptance of the concept of acceptable levels for carcinogenic substances, exemplified in the setting of an admittedly very low MAC (15 micrograms per 100 cubic metres of air) for "the classical carcinogen benzo(a)pyrene." A similar conclusion might be drawn from Dinman's citation of an undated paper by Volkova, to the effect that experimentally derived MACs are "only *indicative*, requiring correction from human experience derived data. From a practical viewpoint we (Dinman) do not believe that there is any significant difference in Western attitudes or emphasis" (84, p. 414; Dinman's emphasis and paraphrasing).

Defining health: judgement and function

A 1975 World Health Organization report on "Early Detection of Health Impairment in Occupational Exposure to Health Hazards" (85) notes (p. 10) that several different criteria of health impairment can be used, including changes in biological and morphological parameters; changes in the physical state and the function of physiological systems; changes in well-being (for example, drowsiness, irritation) to be evaluated through medical histories; and integrative changes that may be produced by effects on several physiological systems. However, the report goes on to emphasize that:

> "Even though different scientific authorities may not fully agree on what should be called 'health impairment,' it can be stated that a *statistically significant effect as such is not the same as impairment of health;* one should therefore distinguish between effects as such and adverse effects, i.e., unacceptable effects. What is regarded as unacceptable (not permissible) is a matter of interpretation and ultimately of choice." (Emphasis in original)

Clearly, here, the social definition of "acceptability" is intertwined with the definition of a health effect.

A joint ILO/WHO report issued in 1977, which drew extensively on the 1975 document, expanded on this theme by noting that "[i]f one considers an effect or response as adverse, then the corresponding dose or level of concentration in air has to be considered not permissible" (86, p. 35). One wonders whether the process may not also operate in reverse—defining the adversity of effects by the conditions which give rise to them.

The linking of scientific and social considerations is further suggested by the typology of effects used in the 1975 report (and reproduced in 1977): effects agreed by general consensus to be adverse (the examples used are an overt dip in the audiogram and an aminolaevulinic acid level of 20 mg/litre in urine); effects that may be considered to be adverse, like decreases in nerve conduction

Defining health: judgement and function *continued*

velocity, unaccompanied by clinical symptoms, in lead-exposed workers; and effects possibly related to exposure and to health impairment, "*but about which there is no consensus*" (emphasis added). Consensus is, of course (like the choice of standard of proof with respect to the second category of effect cited) a *social*, not a scientific process. The WHO report further claims that:

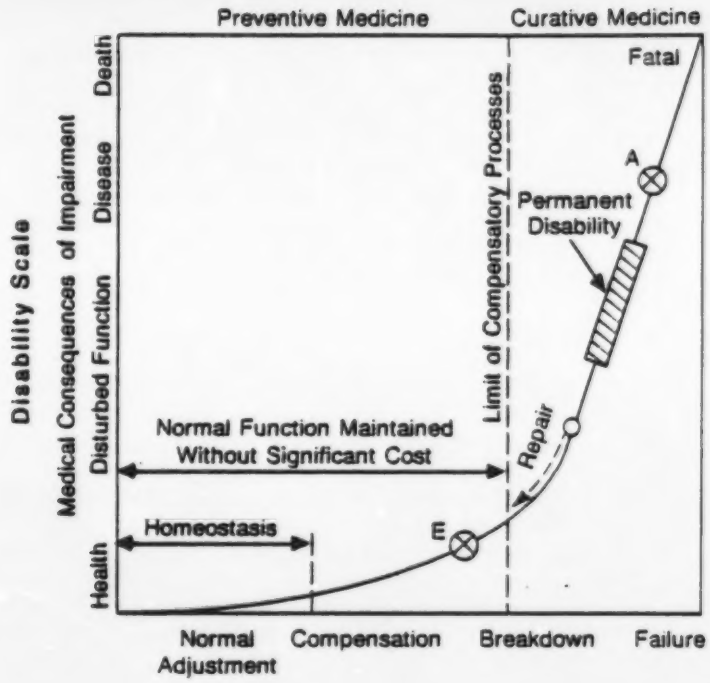
> "...there is usually a continuum: no observed effect — compensatory effect — early effect of dubious health significance — early health impairment — manifest disease."

This was not, it should be emphasized, a new idea. Zapp had noted in 1947

> "...that there is no precise way of defining, except perhaps intuitively, what might be termed a state of good health. We recognize such a state, however, as one in which the individual is able to work and live effectively and without undue strain on his inner resources. We recognize another state of health in which we are able to work and live, but only under a feeling of tension, strain or discomfort. ...Finally, there is a state of health in which excessive changes in the physical, chemical or functional components of the organism cause a definite impairment in the ability of the individual to lead a normal existence." (87, p. 28)

In 1962, Hatch (88) drew the distinction between impairment and disability, and presented the concept of an "impairment-disability curve" in which the horizontal axis represented an impairment scale with gradations ranging from normal adjustment through compensation to breakdown and failure (see Table 3). The vertical axis indicated the medical consequences of impairment, ranging from health through disturbed function through disease and death. The distinction appears to have been highly influential; Hatch was to refer to the concept a decade later, in an article for the *Bulletin of the World Health Organization* (70), and in 1981, Mastromatteo (89) reproduced Hatch's diagram as part of a defence of the concept of threshold, quoting extensively from Hatch's earlier work. The use of a concept like that of the impairment-disability curve in the choice of a threshold or permissible exposure limit clearly implies a substantial element of judgment on the part of the chooser — calling into question Zapp's 1977 implication that the choice of an exposure limit is one which can be defended solely by its scientific correctness. Hatch's own discussion in the 1962 article in which he first described the curve emphasises that the relevance of the curve is, to a considerable extent, a result of historical progress in controlling many hazards whose relationship to frank disease was relatively obvious, and for whose control "[r]elatively crude dose-response relationships [could] be extrapolated downward to provide a basis for...immediate goals."

Figure 3



An historical perspective: the case of lead

The issue of defining ill health and its relation to the sensitivity of particular tests can be put into context by a necessarily cursory examination, based on the TLV *Documentation*, of the history of the lead TLV. Today's TLV of 0.15 mg/cubic metre of air (STEL: 0.45 mg/cubic metre) can be traced to a study of a storage battery plant published in 1933, which concluded (90, p. 31):

> "It is hard to escape the conclusion that the limit of safety under the conditions encountered in this study is less than 1.5 milligrams per 10 cubic metres of air."

The study reached this conclusion on the basis of examining the relation among clinical findings, laboratory findings and workplace lead exposure for two groups of exposed workers:

(a) those receiving workers' compensation for plumbism (lead poisoning); and
(b) "workers who came to the dispensary and whom the plant physician suspected of being leaded. The rate of occurrence of initial visits of this type served as an early index of lead absorption."

An historical perspective: the case of lead *continued*

Some indication of the serious nature of the lead intoxication involved comes from the the 1933 study's description of the symptoms of compensated workers (pp 51-52):

> "Plumbism developed without much change in general appearance, other than perhaps a slight jaundice, especially noticeable on the sclera, and an apparent nervous condition or increased irritability. The more common subacute or chronic form of plumbism, however, was usually accompanied by certain changes in physical appearance. Vasomotor disturbances manifested by pallor and by nervous flushing were usually very evident. A lead line was sometimes present. Because of their listless attitude, stooping posture, apparent loss of strength, evident loss of subcutaneous fat and tone of muscles of expression, these cases presented a picture best described by such terms as 'apparent ageing' or 'premature ageing.' Recovery from an attack of plumbism was often followed by marked improvement in general appearance and the disappearance of this prematurely aged look. Such was not true of those who had suffered repeated attacks of the disease, since the accompanying arteriosclerosis and chronic nephritis were more or less permanent."

These symptoms were much less frequent among the "leaded group" as a whole (as distinct from the subgroup of cases of compensable plumbism), with premature ageing (hardly an insignificant effect) the only symptom reported by more than five percent of the workers in this group as a whole. However, examination of blood and urine samples from workers coming to the dispensary for examination showed a number of changes which did not show up, or showed up much less frequently, in controls (p. 53). The study notes (p. 32) that:

> "Unfortunately no data were available as to the risk of initial visits (to the dispensary) in occupations with exposures lower than 1 milligram per 10 cubic meters of air; but in view of the low rate of plumbism in miscellaneous departments, it is believed that, *except possibly for prolonged exposure*, concentrations below this level (exposure for 8 hours a day) may be disregarded *so far as severe lead poisoning is concerned*." (Emphasis added)

Parenthetically, the cited study was also one of the first to imply a link between institutional racism and occupational hazards: it noted the overwhelming preponderance of black workers (more than 90 percent) in the mixing operation, where the risk of lead poisoning was highest. No other job category had more than one in four black workers, and the lowest-risk jobs had none at all (p. 9).

An historical perspective: the case of lead *continued*

The 0.15 mg permissible limit for lead derivable from the 1933 study was cited by numerous compilers of such values including Bowditch *et al.* in 1940 (78), Cook in 1945 (3), and ACGIH in 1947 (91). In his extensive 1956 article which is the precursor of the current TLV *Documentation*, Smyth (9, p. 164) conceded (based on the 1933 study by Russell et al.) that the 0.15 mg TLV was "low enough to prevent disabling poisoning, but not to prevent some mild cases."

Subsequently, the use of biological concentrations, rather than ambient levels, as indicators of imminent hazard of lead poisoning became widespread. This approach was justified by observations like that of Kehoe in 1961 that:

> "Experience has shown conclusively that lead intoxication does not occur, even in infants and children or in 'unusually susceptible' industrial employees, until and unless the concentration of lead in their blood has reached or exceeded 0.08 mg.../100 g whole blood. ...[W]e have never encountered a single person in whose blood, at the onset of lead intoxication, a lead concentration of <0.08 mg/100 g was found." (93, pp 142-143)

In addition to suggesting the strength of the new emphasis on biological indicators, these quotations also point to the recurring distinction between physiological impacts and actual health impairment which has characterized the lead debate. Implicit is the validity of a distinction between "lead intoxication" and "asymptomatic excess lead absorption" (94, p. 22).

This distinction would appear to be called into question by recent work indicating the presence of subclinical nervous system damage (reduced nerve conduction velocity) among workers whose blood lead levels have never exceeded 70 micrograms per 100 ml. (95) Seppalainen *et al.*, the authors of this work, observe (p. 183) that:

> "It is commonly thought that PbB [blood lead] levels in excess of 70 ug or even 80 ug are obligatory for the development of poisoning. Biochemical changes that do occur at lower lead levels...are often said to be of no clinical importance. Of course, in terms of health, the importance of slight subclinical neuropathy can be questioned, too, and we did not find any evidence that the well-being of these workers was influenced by the neuropathy, *apart from a few complaints of numbness of the arms*. Thus the term poisoning, in its orthodox sense, cannot be applied to these disorders. But neuropathy, no matter how slight, must be regarded as a more serious effect than the quite reversible alterations in heme synthesis, because the nervous system has a poor regenerative capacity...Since the entire question belongs to the diffuse 'gray area' between health and disease, it is more than probable that opinions will diverge.

An historical perspective: the case of lead *continued*

> We think, however, that no damage to the nervous system should be accepted, and that, therefore, present concepts of safe and unsafe PbB levels must be reconsidered." (Emphasis added)

Their opinion does, indeed, diverge from that of the ACGIH TLV committee, which as of 1984 (in its own words) was "not convinced that the biochemical changes found due to low level lead absorption are incompatible with good health" (26). Judgments of this sort obviously go beyond the competence of toxicology as an experimental science, and arguably even beyond that of the diagnostician's art: they are social artifacts rather than biological data.

Risks, benefits and "acceptable risk"

Introduction

Historically, we have — to use Hatch's conceptual framework — gradually been moving downward and to the left on the impairment-disability curve in defining what kinds of effects will be treated as adverse or unacceptable. This is not a "scientific" decision — a point exemplified by Smyth's 1979 discussion of the TLV for benzene:

> "It was first set at 100 ppm, following Winslow's extensive survey of industrial use and worker health. By stages the value has been reduced to 10 ppm. To evaluate the reduction properly, we must bear in mind the details of Winslow's conclusions. He said that 100 ppm was the lowest exposure that engineering know-how of his day could maintain. He said that injury developing in those exposed to 100 ppm (and careful study of his tables shows that he found one-third of them responding adversely) would not be irreversible by the time that periodic medical examination could detect it. Since Winslow's day we have found no new information which defines a lower acceptable level of exposure, but our concept of what is acceptable has changed. It is now practical to maintain concentrations below 100 ppm, but adverse reactions in one-third of those exposed is no longer acceptable..." (96, p. 660)

One may disagree with Smyth's analysis of the emergence of new evidence about benzene while nevertheless granting his general point about the historical context of acceptable risk decisions. The non-scientific nature of these decisions is much more readily admitted at some times than at others. Two of many ways in which this admission sometimes surfaces are important enough in contemporary workplace health policy and practice, though they have been around for some time, to merit further discussion. One is the choice of an exposure standard on the basis of a decision to accept a certain specified (usually statistical) risk. Alternatively,

Introduction *continued*

and sometimes as part of the same process, a conscious or explicit weighting of risks against benefits may be involved.

Choosing an acceptable risk

Criteria of the acceptability of risk have often been incorporated into scientific investigations without an acknowledgement of their nature. One example dealing with the acceptability or seriousness of eye and respiratory tract irritation illustrates the implicit adoption of such criteria. The experiments of Nelson *et al.* to determine the irritant effects of various substances on human subjects formed the basis for several of the values in Cook's 1945 compilation of acceptable concentrations. According to the report of these experiments, "each person was asked if he believed he could work in the atmosphere for an eight-hour day" and "[t]he amount of vapor which the majority of subjects rejected as a working atmosphere was termed objectionable, and the next lower concentration tested was therefore taken as a tentative practical limit." (97, p. 282)

Cook, in many cases, took as an acceptable concentration a value *higher* than that which irritated a majority of subjects: for example, he recommended a permissible exposure limit of 500 ppm for acetone, and 200 ppm for xylene, although Nelson's subjects estimated the highest satisfactory concentrations as 200 and 100 ppm, respectively. There is, to put it mildly, little of science in these choices of one value over another.

The "comfort" criterion of the Committee on Chemical Agents (56) is a form of numerical statement of acceptable risk: that concentration which in a short time is not objectionable to 9 out of 10 unacclimatized individuals. In the literature surveyed for this report, the first specification of an acceptable risk criterion expressed in definite numbers for a non-irritant effect occurs in the British Occupational Hygiene Society's 1968 proposal for a hygiene standard for chrysotile asbestos dust, in which the Committee said "that it is reasonable to reduce to 1 per cent the risk of getting asbestosis through having worked for a lifetime with asbestos" (98). The Committee took a similar approach in proposing a cotton dust standard in 1972, in that case suggesting that a prevalence rate of four cases in 100 of grade II byssinosis due to airborne dust among those individuals who work in the dustiest conditions (99) represented an acceptable risk.

The specification of an acceptable risk in numbers has subsequently become widespread in the environmental health field. The concept's credibility in the occupational area appears to be more limited, although the International Commission on Radiological Protection (ICRP) has proposed that the current mortality rate from work-related illness and injury in "safe" industries represents an acceptable risk for purposes of setting radiation exposure

Choosing an acceptable risk *continued*

standards (100). Ontario's Ministry of Labour appears to be one of the few standard-setting bodies to have adopted this approach: the province's vinyl chloride standard was set by comparing a quantitative cancer risk estimate derived from animal data with the ICRP's numerical estimate of an acceptable human cancer mortality risk (101, pp 20-44). And Dutch authorities have suggested that the one per cent or five per cent response level for an exposed population may designate an exposure corresponding to an acceptable risk, although it is not known whether this criterion has been applied to specific substances (102, p. 274).

Much more frequent is the contention that risks imposed on workers should be assessed (and can be justified) in terms of corresponding benefits to "society". One of the earliest accounts of a debate on this topic within what might be called the standard-setting community is Alice Hamilton's account of a 1925 conference in Washington, D.C. on the dangers of leaded gasoline to workers.

> "It was evident at once that the conference was between two groups. The first was composed of those who held that the use of tetra-ethyl lead in gasoline is of great public advantage because of the conservation of gasoline which it makes possible, with them a number of laboratory men and public health officials who believe that all evidence of harm to human beings from the distribution and use of ethyl gasoline is lacking after two years of use in at least 20,000 filling stations and that animal experiments have shown no lead poisoning from exposure to exhaust gases. Opposed to these were physiologists, toxicologists, physicians and public health officials who maintain that no conclusive investigation has ever been made, that the animal experiments are insufficient and that even if they were conclusive they could not be accepted as applying without reserve to human beings." (103)

In response to a Dr. Touart, who argued that "the burden of proof should be on the industry to demonstrate that ethyl gasoline was not harmful instead of on the medical profession to show that it was," a representative of the Standard Oil Company defended "ethyl gasoline as a discovery of the utmost value to the public, necessary for the conservation of motor gasoline not only in this country but also in Europe."

A cost-or risk-benefit perspective is evident from other sources, as well. In a 1971 article on standard-setting in environmental protection, Stokinger (then, it should be recalled, the Chairman of ACGIH's TLV Committee) warned against excessively strict standards:

> "Heavy industry, unable to survive on repeated annual financial losses or to continue on less than a 4 to 6 per cent

Choosing an acceptable risk *continued*

profit margin, will ultimately pass the needless charge on to the consumer." (104, p. 665)

In 1974, Stokinger made clear the connection between cost-benefit considerations of this sort and the definition of health, arguing that:

> "It is not enough merely to define the dose that will produce a borderline response. The next important step is to determine whether the response at the defined dosage has any over-all *physiologic significance to the industrial worker*, who is on the job day after day, and may become inured through homeostatic mechanisms. ...Not to make the determination of physiologic significance can result in undue alarm for health and safety of the worker and, more importantly, can result in costly over-engineering — costs that are ultimately passed on to you and me, the consumer." (41, p. 20: emphasis in original)

If the definition of health is not actually a function of what industry (and society) feel they can afford, it *becomes important in that context*. An implicit weighting of risks against benefits is suggested by Truhaut's contention, in discussing the question of thresholds for carcinogens, that:

> "Among the parameters to be taken into account in making a *toxicological* evaluation, *in addition to scientific facts*, are practical considerations such as the irreduceable environmental background level and the benefit of use for the community, as adequately evaluated by, as much as possible, objective criteria." (105, p. 690; emphasis added)

Implicit risk-benefit weightings of this sort become tremendously important when the issue is that of *how much evidence is enough* to demonstrate the existence of a particular health effect (106, p. 6-11). As an example, the so-called Delaney clause of the U.S. Food, Drug and Cosmetic Act provides that "no (food) additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal..." (cited in 107, p. 109). Darby (107) has noted in a discussion of the Delaney clause that:

> "The [risk-benefit] assessment may be included implicitly (and perhaps, unknowingly), when the decision-maker acts only upon experimental evidence which is acceptable to the scientific community. In this case, the decision-maker accepts the assessment which is contained in criteria established by the scientific community for judging experimental results. Neither the experimenter nor the decision-maker may be aware of the particular assessment, which underlies the so-called 'purely scientific' decision. ..."

Choosing an acceptable risk *continued*

Thus, the use of scientific standards of proof embodies a strong presumption *against* regulation of potentially dangerous substances when the information base is inconclusive. And the Delaney clause emerges as an implicit and unexamined decision rule for risk-benefit balancing, that is, as a framework within which risk-benefit decisions are to be made rather than a legislative embodiment of a zero-risk philosophy.

> "Given an explicit risk/benefit assessment in which the risks far outweigh the benefits, a decision-maker would probably ban a substance based on evidence of carcinogenesis *which would not be significant enough to be accepted by the scientific community* and which might not trigger the Delaney Clause mechanism." (107, pp 116-117; emphasis added)

In this case, making decisions on an explicit risk/benefit basis might lead to stricter, rather than (as is often assumed) less strict control of hazardous substances!

Strength-of-evidence decisions are an extremely important component of the setting of permissible exposure limits. For this reason, the institutional context is crucial. To whom do the standard-setters listen? What are the values they bring to the process? It is worth quoting at length from a 1969 paper (36) by Stokinger on the procedures used by ACGIH's Threshold Limit Values Committee to reevaluate existing TLVs:

> "Procedures used by the committee take three forms: (1) the chairman and members of the appropriate subcommittee hold a meeting with industry's physicians and industrial hygienists and review their experience. This procedure is used where the data has *(sic)* not been assembled or published. ...(2) Where the data or reports have been published, these are reviewed by the chairman and the committee and the action taken that is that mutually agreed upon by industry and American Conference of Governmental Industrial Hygenists by letter correspondence. ...(3) Active cooperative projects with industry...are entered into whereby industry supplies the health records or clinical data for review, or active toxicologic research investigations are made...in conjunction with clinical and environmental data obtained by industry."

In addition, "industrial hygenists and toxicologists of some companies serve as consultants to the Committee ensuring first-hand information and knowledge." (58, p. 11)

This consultative procedure may have its origins in the period in which consultation with employers and the use of moral suasion were virtually the only avenues open to industrial hygienists. Its advantages, according to Stokinger, include access to "[s]tatements derived from the long experience of the medical directors of the

Choosing an acceptable risk *continued*

companies that normally would never get to the attention of the committee [which are] elicited in amicable discussions." This represents, of course, a clear departure from the norm of full, open and scrutable publication of scientific results. Perhaps more seriously, such heavy reliance on consultation with industrial hygienists and physicians may tend to reinforce a high degree of reliance on human evidence obtained from medical surveillance. And it suggests that the risk-benefit component of the standards which emerge is implicit and inscrutable — a suspicion reinforced by Stokinger's 1981 reference without further explanation to the TLV Committee's success in "dealing with occupational carcinogens in a manner industry can live with" (58, p. 8).

Permissible limits for carcinogens?

The setting of occupational exposure standards for carcinogens has been the topic of some of the most persistent criticisms by labour of government, and of non-governmental bodies like ACGIH. Only in 1962 did ACGIH acknowledge the special nature of carcinogenic effects by establishing an appendix to the TLV list comprising "carcinogens and other substances whose limits [can] not be described with a single value." (74, p. 73). And ACGIH (like other standard or guideline-setting bodies) still appears not to have come to grips with the implications of establishing permissible exposure limits for carcinogens.

Deciding what should and should not be treated as a carcinogen is itself a subject of considerable controversy. Positive epidemiological studies are generally afforded the greatest weight, but there is less agreement on the strength of evidence which should be required for identifying carcinogens from animal tests. The International Agency for Research on Cancer considers as "sufficient evidence" of carcinogenicity in animals results from multiple experiments, experiments with multiple species (to answer the objection that some positive results reflect the extreme susceptibility of a particular species), or experiments which show a very high or unusual incidence of cancer. IARC's position is that, in the absence of conclusive epidemiological evidence, chemicals for which there is sufficient evidence of carcinogenicity in experimental animals should be regarded as if they presented a carcinogenic risk to human beings. IARC warns that "at the present time a correlation between carcinogenicity and possible human risk cannot be made on a purely scientific basis, but only pragmatically" for the purposes of regulatory agencies "in making decisions related to the primary prevention of cancer." (108)

The IARC statement represents a significant area of conflict in the weighting of uncertainty, in which the scientific merits of inferences about the similarity of mechanisms of cancer causation among species should not be confused with the inherently social character of a permissible exposure limit based on a resolution

Permissible limits for carcinogens *continued*

of this issue. As Darby's (107) comments suggest, the question becomes one of the relative desirability of being wrong in two different kinds of ways (that is, acting on false negatives and false positives in the identification of carcinogens). The question is made more significant because absence of positive evidence from studies of human subjects often cannot be taken to indicate absence of risk.

A 1981 survey (109) of US firms manufacturing, processing or using the 75 substances classified by IARC in 1979 as confirmed animal (but not human) carcinogens found that epidemiological studies were available or under way for only eight of the 75 substances. For many such substances, it appeared that epidemiological investigations would be either impractical or of limited scientific value, suggesting that, quite apart from the ethics of continuing to expose workers to suspected carcinogens, a demand for epidemiological evidence constitutes a *de facto* decision that a substance will not be treated as carcinogenic for purposes of determining permissible exposure. And what can be demonstrated by epidemiological studies is often limited: a recent review of the statistical power of occupational mortality studies (their ability to detect an actual underlying excess risk) notes that because of limitations which are a function of sample size, the actual magnitude of the excess risk, and the expected incidence or mortality,

> "...a large proportion of SMR studies have a low probability of detecting...an increase in the incidence of disease or of cancer at predicted sites of 50% above that among unexposed subjects." (110, p. 606)

Thus the demand for epidemiological evidence of carcinogenicity implies accepting a probability of false negative results (failures to find a statistically significant excess of cancers) which may be very high.

The interrelated questions of determining dose-response relations and the presence or absence of thresholds are even more problematic. The difficulties of assessing dose-response relations at exposures to carcinogens comparable to those which human beings might encounter in the workplace or the environment are amply illustrated by a study involving a total of more than 24,000 mice exposed to the acknowledged carcinogen 2-acetylaminofluorene (2-AAF). Its objective was to discover the effective dosage which would produce a one per cent tumor incidence and to enable experimenters "to study the shape of the dose-response curve with precision about one order of magnitude greater than that generally obtained from current carcinogenesis screening studies" (112, p. 3).

One per cent is still a high rate of (increase) in lifetime cancer risk in an exposed human population, yet it is also a much lower

Permissible limits for carcinogens *continued*

increase than could normally be detected in a standard laboratory test or in epidemiological studies.

Bladder tumors among exposed mice showed an extemely steep dose-response curve which superficially suggests the existence of a threshold; however, "non threshold models also fit the available data." This is a common problem in the much smaller-scale animal experiments normally used to test for carcinogenicity (111, 112). And "[a]s time was extended, bladder tumors appeared at lower dosages with no indication of a threshold within the limits of observation of the study. ...*Even with these large sample sizes we can be confident only that the lifetime bladder tumor rate at 30 ppm*", the lowest dosage tested, "*is less than 9 per 1000, certainly not the equivalent of a threshold effect.*" (113, pp 180-181; emphasis in original)

A "cautious", linear extrapolation at the low end of the dose-response curve for bladder tumors yields a predicted upper limit of risk of one in a million at an exposure of 10 ppb. This dosage

> "...is 3000 times lower than the lowest level of 30 ppm used in the study. Some people argue that tests should be conducted at human exposure levels. If risks at these levels were on the order of one per million, several million animals per test would be required to determine if a carcinogenic risk existed. Even testing at 100 times the allowable level is not sufficient to insure adequate safety. Hopefully, the risk at 100 times the allowable dosage would be low, possibly requiring thousands of animals to detect such risks." (Id.)

The dose-response curve for liver tumors among exposed mice "was observed to be nearly linear, indicating absolutely no tendency for a threshold dose." Further, the pattern of liver tumor incidence suggests a major weakness of common experimental designs:

> "For animals sacrificed at 18 months, liver tumors were observed in 5.8% of the animals at the highest dosage level tested. Had a typical number of 50 animals been used, and had the study been terminated at 18 months, which is not uncommon for safety tests using mice, liver tumors would have gone undetected. Thus, the tumor endpoint which posed the greatest risk at low doses would have been overlooked. In fact, even bladder tumors would not have been detected by 18 months with 50 animals except at the highest dosage of 150 ppm... ." (113, p. 182)

The "megamouse study", as it has been called, demonstrates three crucial points: the need to test at high doses of suspected carcinogens if any useful information at all is to be obtained; the virtual impossibility of proving or disproving the existence of

Permissible limits for carcinogens *continued*

thresholds in experimental situations; and the need for considerable skepticism about negative experimental results (as about negative epidemiological studies). The issue of thresholds must therefore be decided, at the scientific level, on the basis of a series of indirect inferences from experimental results which, however convincing, are not the same kind of conclusion that could be reached on the basis of direct experimental evidence.

Truhaut (105, 114) has succinctly catalogued the various arguments for and against the existence of thresholds at least for some carcinogenic substances, one of the more telling points being that for some carcinogens, an effective threshold may exist if the minimum time before the incidence of a tumor is longer than the life of the human species. A point of particular importance in discussions of permissible exposure limits is Truhaut's observation (based on the deliberations of a WHO working group) about the difficulty of determining a threshold *for a population* (105, p. 689) as opposed to positing the existence of a threshold in a particular, individual organism. Rall has made this observation as well, and has also pointed out that in standard-setting "the issue is not thresholds or no thresholds; it is one of adding a new carcinogen to a pool of present carcinogens" (115, p. 164).

The foregoing discussion is an exceedingly brief overview of some of the uncertainties involved in determining cancer risks in exposed human beings. Examining the TLV *Documentation* (26) provides an interesting view of how a particularly influential institution has dealt with them in practice. ACGIH has set a TLV of 2 ppm for acrylonitrile, regarded as a suspected (not proved) carcinogen on the basis of positive animal studies and both positive and negative epidemiological findings. ACGIH considers benzene only a suspected carcinogen as well, noting that evidence of its leukemogenicity in human beings is based on exposures considerably higher than the current TLV of 10 ppm (STEL: 25 ppm). ACGIH quotes the TWA of 10 ppm as the recommendation of a 1976 international workshop, with the proviso "that benzene should not be employed when substitute materials were available," and ACGIH contends that in the absence of much evidence of blood damage from concentrations of 25 ppm, the TLV actually provides a margin of safety.

Coal tar pitch volatiles are treated as a "recognized carcinogen," as a result of epidemiological studies of coke oven workers. A TLV of 0.2 mg of the benzene soluble fraction per cubic metre of air is justified with the simple statement that it represents "the most practical compromise" and that if it is complied with "any increase in the incidence of lung and other tumors, due to occupational exposure, should be minimal." Vinyl chloride, another "recognized carcinogen," carries a TLV of 5 ppm; despite an acknowledgement of the difficulty of deriving a TLV from epidemiological studies on exposed workers, "[i]t is the sense of

Permissible limits for carcinogens *continued*

the Committee that, if the average exposure to vinyl chloride does not exceed 5 ppm, there will be no increase in the incidence of cancer, specifically of angiosarcoma of the liver. It is probable that the cancers reported and attributed to vinyl chloride among PVC workers resulted from exposures many times this level." This approach contrasts with regulators' treatment of vinyl chloride in Ontario, where as noted previously a numerical risk estimate was calculated based on animal data.

These four examples are just that, and the literature reviewed in the *Documentation* for these four substances has not been surveyed for this report. The *Documentation* implies however, that the TLV Committee has not taken a consistent approach to the basis on which (if at all) permissible exposure limits for carcinogens should be set. For four recognized human carcinogens, ACGIH sets no TLV and specifies that "no exposure or contact...shall be permitted". For others, and for many of the substances it terms suspected carcinogens, TLVs are set. In the case of coal tar pitch volatiles, the TLV involves a clear acceptance of a "minimal" (but unspecified) level of risk. In the cases of vinyl chloride, benzene, and acrylonitrile, *the existence of a population threshold is implicitly assumed.* Without reviewing the literature underlying these recommendations, it is impossible to come to a specific conclusion about the validity of this assumption. In general, however, it would seem to ignore the warning quoted by Truhaut.

Henschler has noted that in West Germany:

> "...a different category of standards for occupational carcinogens has been introduced as 'technical guidance concentrations' (TRK) which are based on the political, socio-economic and technical decision-making processes, with the only scientific element in the argumentation being that adherence to the respective level might reduce risk as compared with a state of no regulation at all. But this type of standard should by no means be confused with the conventional exposure limit (TLV, MAK, etc.) which is based on *a well definable philosophy of safety evaluation*." (32, p. 69; emphasis added)

The treatment of carcinogens is only one of several "compromises" isolated by Henschler in the setting of permissible exposure limits, and it should not be inferred from this comment that he views the enterprise as purely scientific except with respect to carcinogens! But his comment does suggest that the lack of a "well definable philosophy" on the part of ACGIH reflects a broader reluctance to admit the depth of scientific uncertainties and the social nature of permissible exposure limits. Confronting the issue of exposure limits for carcinogens drives this latter point home, because the effects of reduced exposure are manifest not as less serious effects, but as fewer effects or as a longer time before the appearance of

Permissible limits for carcinogens *continued*

the effect (116). Hence, setting permissible limits for carcinogens while denying or questioning the existence of thresholds represents a much more overt acceptance of clearly serious consequences than does the activity of limit-setting with respect to some other kinds of effects.

Standards for the individual worker: safe-person strategies

Introduction

At the risk of some oversimplification, it is possible to distinguish two related characteristics of the increasing contemporary emphasis on preserving health in the workplace by focussing on the exposed individual worker. The first of these is the growing attention to physiological or behavioral changes in the individual worker as an indication of hazards or potential hazards from exposure to chemicals or physical agents. The second involves research efforts aimed at detecting the extent to which particular individuals or identifiable groups may be more vulnerable than others to the effects of a particular chemical or physical agent ("hypersusceptible" individuals).

Recommendations that workers be monitored for the effects of substances known, or strongly suspected, to be toxic are nothing new. The earlier-cited National Safety Council study on benzene poisoning was quite specific in its recommendations for engineering controls and substitution of less toxic solvents, but it further recommended that

> "[t]o detect incipient benzol [benzene] poisoning at a stage when its effects can be minimized, it seems essential...that all workers to be employed in processes where exposure to the fumes of this solvent is involved should be given a thorough medical examination before employment and should be reexamined, with systematic blood counts, once a month thereafter."

The study recommended that "*[n]o worker should be employed in a benzol process*" (emphasis added) who showed signs of organic heart, lung or kidney disease; anemia; or hemorrhagic tendencies. And its authors went on to note that:

> "Any worker who, on reexamination, shows any of the following symptoms should be promptly excluded from benzol exposure and transferred to some other department of the industry:
>
> a. Hemorrhages from the mucous membranes of the nose, mouth or other organs;
> b. Decrease of more than the following amount from the employee's normal blood picture (normal conditions will be obtained from previous examinations of the individual

Introduction
continued

employee); *white cells*, decrease of 25 per cent; but in no case should an employee with a white cell count of less than 5,000 be continued in benzol processes; red cells, decrease of 25 percent; *hemoglobin*, below 70 per cent." (21, pp 70-71)

Nor is attempting to determine the characteristics of the worker for purposes of health protection a new phenomenon. Hamilton (22, pp 6-13) recounts a number of pre-1925 attempts to determine the relative susceptibility of women and men, or of white and black workers, to occupational lead poisoning and other industrial diseases. She also emphasizes variations in individual susceptibility to the effects of workplace poisons, and the political import of this phenomenon (p. 15). And Omenn cites J.B.S. Haldane, writing in 1938, to the effect that:

> "[W]hile I am sure that our standards of industrial hygiene are shamefully low, it is important to realize that there is a side of the question which so far has been completely ignored. The majority of potters do not die of bronchitis. It is quite possible that if we really understood the causation of this disease we should find out that only a fraction of potters are of the constitution which renders them liable to it. If so, we could eliminate potters' bronchitis by regulating entrants into the potter's industry who are congenitally exposed to it." (117, p. 370)

Zapp, in 1947 (87), argued the importance of both pre-employment screening and ongoing biological/medical monitoring:

> "[I]t would appear important to do at least three things: (1) specify that the health of the workers shall come up to certain standards before they are employed on an operation involving exposure to chemicals; (2) specify to the best of one's ability the conditions under which the operation should be safe...and (3) inspect the workers periodically to determine whether or not deterioration of health has taken place, and if so, from what causes.

He proposed the use of periodic measurements of blood pressure to provide an early indication of toxic effects on exposed workers, noting that the test itself was quick and simple. The rationale for such an approach was broadly the same as that advanced by Zapp for protection of workers' health in general: "it is important," wrote Zapp, "to detect variation in the health of the worker before the variation becomes create enough to be considered pathological, resulting in lost time and productivity." (87, p. 30) As early as 1955, Stokinger (59) suggested that a

> "...feature of occupational health standards that appears destined to play a useful role in evaluating personnel exposure

Introduction *continued*

> in industry is what might be called biological threshold values, for want of a better term. These values refer...to the greatest *permissible* content of an air contaminant or its metabolic derivatives in the body fluids, usually in blood or urine..."

Stokinger also argued the importance of "tests of pretoxicosis, the detection of subtle metabolic changes in the body *before injury* of serious proportions has developed." In both the preceding quotations, the emphases are added, serving to highlight the connections among biological criteria, definitions of health, and specification of acceptable or tolerable impacts on the human organism.

"Hyper-susceptibility"

Hatch, in 1962, suggested the historical background against which to view the issue of hypersusceptibility:

> "Differences in individual susceptibility are always recognized as factors which may influence dose-response relationships but the influence is largly submerged when the hazard is high. Again, as progress is made in control, a point may be reached finally where the risk of ill-health depends more on the status of the host than it does on the conditions of exposure." (88, p. 3)

Green (75) has noted the efforts of Herbert Stokinger and others between 1962 and 1973 to develop and promote biological monitoring techniques which were aimed at detecting the hypersusceptible worker. By 1973, Stokinger was able to report the development of tests for five genetic abnormalities linked to specific industrial exposures:

- hereditary serum antitrypsin deficency (linked to increased risk of pulmonary emphysema);
- glucose-6-phosphate dehydrogenase deficiency (G-6-PD), which increases susceptibility to the hemolytic effects of a great many workplace pollutants including aniline, arsine, benzene, carbon tetrachloride, lead, methylcellosolve, nitric oxide, and phosphorus;
- reduced capacity to metabolize tetraethylthiuram, which was believed to indicate enhanced susceptibility to carbon disulphide intoxication;
- immunologic characteristics believed to indicate particular vulnerability to the sensitizing effects of isocyanates;
- sickle-cell trait and sickle-cell anemia which, it was argued, might put the individual in question at excess risk in a number of industrial situations. (118)

"Hypersusceptibility" *continued*

It was argued that such tests effectively increased the degree of protection provided by permissible exposure limits. "[T]here is no provision in many, if not in most, industrial air standards...that assures protection of all workers; the hypersusceptibles commonly respond to exposures well below the limits set by the standards." (118, p. 564)

Several factors suggest that the motivations behind increased emphasis on hypersusceptibility screening are economic, at least in part. About testing for abnormal sensitivity to isocyanates, for example, Stokinger and Scheel note that "it is *not possible* at all times to control isocyanate exposure below permissible industrial air limits..." (118, p. 569) Possibility in engineering is very much more a question of economics than of natural law. It appears likely that an undoubtedly genuine concern with workers' health is being tempered by the perceived economic imperative of avoiding over-regulation or over-engineering — a theme which comes up frequently in Stokinger's work of this period (for example, 41, 104).

More seriously, the validation of at least one test (for hypersusceptibility to carbon disulphide) was proposed by means of a "prospective study of individuals before and after exposure to CS_2 and under situations where environmental conditions are accurately known." (118, p. 569) With such a notoriously neurotoxic substance as carbon disulphide, this clearly amounts to a continuation of the great human experiment — again, presumably motivated at least in part by economics.

A further intriguing aspect of the proposals made in 1973 concerns sickle-cell anemia as a risk factor:

> "Although no reports of the adverse interaction of industrial chemicals in workers with sickle-cell abnormalities have come to the authors' attention, it would seem that the following five situations would speak for its inclusion in the pre-employment examination: Exposures to (1) anemia producers, eg, benzene, lead, cadmium; (2) methemoglobin formers, eg, aromatic amino and nitro compounds; (3) Blood oxygen tension reducers, eg, carbon monoxide and cyanide; (4) the concurrent presence of G-6-PD deficiency and sickle-cell abnormalities; and (5) great physical exertion." (118, p. 572)

One would have expected particular caution on this score, in view of the racial implications, but no such caution was shown by Stokinger and Scheel. Did they really propose to screen eight per cent of the American black male population (119) out of the occupational exposures listed?

We come now to perhaps the most important point in the discussion of hypersusceptibility and permissible environmental exposures.

"Hyper-susceptibility" *continued*

What, exactly, is meant by hypersusceptibility? Is this a term amenable to precise scientific definition? Could it be argued (the author is frankly out of his depth here) that it is in some cases, where the trait involved can be defined in an "on-off" manner (for example, the absence of a particular enzyme system) or symptomatically (for example, hemophilia)? In other cases the characteristic involved is not amenable to definition in such a clear-cut manner. For example, the test discussed earlier for abnormal susceptibility to carbon disulphide relies on the rate at which a tested individual metabolizes a particular compound, from which observation we would expect gradations in the rate of metabolism and, hence, in the resulting (hyper)susceptibility.

In situations like these, the definition of hypersusceptibility cannot be a purely scientific one. It also contains elements of an acceptable risk criterion: What percentage of the population do we wish to protect? The definition could in an extreme case become entirely social (without appearing to be so): hypersusceptibility would be defined as a response more severe than that predicted on the basis of exposure at or near the permissible exposure limit.

The definition of hypersusceptibility is also, it appears, not subject to anything like the same strength-of-evidence criteria which are applied to environmental/occupational exposure standards. The need for standards to be based on "scientific fact," and the importance of corroboration from human experience, are axiomatic in the literature (for example, 104). Yet the recommendation to screen for sickle cell trait quoted above is made in the absence of such corroborating experience, on the basis of general statements about the "probability of added health risk in at least five industrial situations" (118, p. 572). It is doubtful that an environmental exposure standard would ever be set on such a basis, because of the economic factors mentioned earlier. Screening out potentially vulnerable workers, on the other hand, is a strategy with few apparent costs to industry other than the cost of the testing itself. Definitions of hypersuceptibility for screening or job placement purposes represent standards, of sorts: standards which measure the suitability not of the work environment, but of the worker. The discussion in this paragraph illustrates, in a context different from that of previous sections of the report, the value-laden nature of strength-of-evidence decisions in standard-setting.

The preceding paragraphs appear to have picked on Herbert Stokinger rather intensively. This may be reasonable, historically, because of his influential status within the industrial hygiene and occupational health professional communities. An article published in 1983 serves both to justify some of the statements made here and to expand on them. Miller (120) concludes in a detailed review of legal and political considerations surrounding the use of biological monitoring both before and during employment that:

"Hyper-susceptibility" *continued*

> "Biological monitoring could...be used to screen susceptible people from the work force at the outset. Employers are usually reluctant to hire workers, if they can avoid it, who can be predicted to cost them money in terms of future illness. Hiring policies could obviously be structured in accordance with the results of comprehensive pre-employment biological monitoring to achieve this end." (p. 398)

And, further on, Miller observes:

> "The most efficient way for management to maintain a healthy workforce is to avoid hiring employees known to be susceptible to occupational illness. ...Biological monitoring offers management an extremely useful tool for predicting which employees constitute special risks for developing occupational disease... ." (pp 412-413)

The susceptible (or hypersusceptible) worker, then, represents a potential cost which managements are anxious to avoid, and genetic screening represents one possible way of doing so. Stokinger and Scheel (118) commented in 1973 that "the reception from industry has been unbelievably bad" for the most part. But the combination of high unemployment and stricter working exposure standards (or, more relevantly, stricter enforcement of existing standards) may be expected to increase interest in this approach to setting standards, albeit slowly.

Biological monitoring of exposure

The theoretical attractiveness of biological monitoring of levels of a workplace contaminant in the worker's body, either directly or via monitoring concentrations of a metabolite, is frequently noted in the literature. In 1950 it was observed that:

> "If there exists sufficient knowledge of the behavior of a chemical in the body, the estimation of one of its metabolites may yield a better approximation of the degree of a workman's total daily exposure than can a time-weighted average exposure... . Physiologic tests, when sufficiently precise, may supplement hygenic standards of exposure, and in so doing avoid the present uncertainties about the 'average man' by determining the degree of response of each exposed person." (56, p. 607)

In 1955, Connecticut's chief industrial hygienist observed that:

> "For some time, the measurement of carbon disulfide, metals and some of the alcohols in body fluids has been used as an index of absorption and exposure, as has the ratio of inorganic to total sulfates in the urine as a measure of benzene absorption

Biological monitoring of exposure *continued*

and exposure, and the formation of carboxyhaemoglobin in the case of carbon monoxide. ..."

and went on to cite a number of contemporary developments in the field (121). A much more recent (1979) review of concepts used in permissible exposure limits noted that biological monitoring "integrates the exposure over time, which is difficult to determine by environmental monitoring." (102, p. 270) A corollary here is that biological monitoring could be seen as a way to overcome some of the uncertainties surrounding the concept of time-weighted average — specifically the questionable assumption of a constant response at varying combinations of concentration and time. Another attraction involves reducing the uncertainties surrounding the variability of response within the exposed population by measuring that response directly.

These are not the only aspects of biological monitoring which appeal to many of its proponents. An additional characteristic of importance is the ability of biological monitoring to provide information on total exposures, including intake of chemicals via absorption and ingestion as well as non-occupational exposures, making it arguably "superior to measurements of workroom air as an indicator of individual risk" (122). Still another is the potential to eliminate the perennially vexing problem of extrapolation from animal studies to human responses. How much simpler to measure human response directly against human biological indicators!

At the same time, for substances which are absorbed and eliminated fairly rapidly like organic solvents, "[r]apidly changing concentrations in body fluids complicate the interpretation of data and the average body burden of a chemical attained during a work shift can easily be over-predicted or under-predicted. Furthermore, biological measurements fail in most instances to detect transient periods of over-exposure during the work shift." (26, p. BEI-1) So the use of biological monitoring runs into some of the same difficulties posed by variable exposures in the context of TWAs. And, so far, reliable biological monitoring techniques are available only for a limited number of contaminants (122).

In one respect, biological monitoring may be seen as an outgrowth or extension of more traditional modes of medical monitoring such as pulmonary function testing which are not ordinarily viewed in the context of permissible limits. However, the setting of quantitative maximum recommended levels for a number of toxic substances or their metabolites (including cadmium, lead, xylene, mercury, and toluene) by the World Health Organization (122, p. 189) clearly suggests the emergence of biological limit values in parallel with permissible environmental concentrations as indicators of risk (and parameters of acceptable risk). A reference to "Biological Limit Values" has, indeed, appeared in the preface

Biological monitoring of exposure *continued*

to ACGIH's TLV list at least since 1973 (62), although no such values were specifically proposed by ACGIH until 1984.

ACGIH has now proposed the establishment of a limited number of

> "Biological Exposure Indices (BEIs) (which) represent warning levels of biological response to the chemical, or warning levels of the chemical or its metabolic product(s) in tissues, fluids, or exhaled air of exposed workers...*Introduction of the BEI is a step in the evolution of the concept of TLVs.* The BEI provides the health personnel with an additional tool to provide protection for the worker. ...Lead is a classical example of a substance for which blood concentrations have long been considered the critical value in determining 'safe' versus 'unsafe' exposures." (26, p. BEI-1)

The extent to which the establishment of "acceptable" concentrations of lead in blood represents a choice of the degree of effect on the human organism considered to be adverse has been discussed earlier. Examining the case of carbon monoxide, one of the substances for which a BEI is being proposed, further underscores this observation.

"Safe" levels of carbon monoxide?

The mechanism of carbon monoxide intoxication (binding with hemoglobin produces carboxyhemoglobin (COHb) and progressively more severe levels of hypoxia as carbon monoxide concentrations and, therefore, COHb levels increase) suggests some serious difficulties in establishing permissible exposures. DuBois (123, p. 427) has observed that:

> "We have to ask whether there is any really safe level of CO. If there were, one would look for a 'threshold,' or level below which no adverse effects occurred. Three studies on neurological function have shown a response to CO proportional to the CO concentration and extending straight back toward zero disturbance at zero concentration in the inspired air, but proportional on upward from zero. ...It seems that CO does not have a 'hockey-stick' dose-response curve — one that would be initially flat, reach a threshold, and then rise — but instead, a line or curve that passes through the origin of axes. *We should then...ask: How much decrement in function are we willing to tolerate under conditions of public exposure for a specified time at a given concentration profile and in specified locations?*" (Emphasis added)

ACGIH notes in the documentation for the carbon monoxide TLV that HbCO levels of 3-5 percent (as against a natural level of 0.4 to 0.7 percent) will impair cardiovascular function in patients with cardiovascular disease and in normal subjects. Yet the BEI

"Safe" levels of carbon monoxide? *continued*

for carbon monoxide has been proposed as 8 per cent COHb (a level which should not be exceeded at the end of a work shift or at any time during it), with the summary observation that "CO does not appear to have *large* and *consistent* behavioral effects on healthy young volunteers with COHb below 10%" (emphasis added); the admission that carbon monoxide exposure may reduce vigilance and ability to do hard physical work at levels below 5 percent; the judgment that this effect may result in impairment of performance but not necessarily impairment in the health of the worker; and the final caveat that the BEI is determined with reference to acute effects only because of the lack of information on chronic effects (26, p. BEI-5).

Yet it is at least a reasonable conjecture (as reasonable as those quoted earlier about sickle-cell trait) that years of mild hypoxic stress of the sort which might be anticipated as a result, for example, of working as a toll booth operator (124) could have a significant effect on health.

Deciding on permissible levels of either airborne concentration or biological response for carbon monoxide (as for other substances) represents a judgment about the seriousness and acceptability of a particular set of effects on the organism. If this were the "bottom line" with respect to biological standards, they could be dismissed merely as another manifestation of the quest to limit uncertainty by the institutionalization of numbers. But they cannot be dismissed so easily because they have a number of additional implications which are problematic, if not sinister.

Biological monitoring: some further implications

First, one can predict the growth of a tendency to use biological limits as indicators of the presence or absence of toxic/unacceptable effects in *individuals*, even when their importance has been demonstrated on the basis of correlations between levels of the biological indicator and particular symptoms in a *group* of workers whose individual susceptibility may vary widely. Seppalainen *et al.* (95) specifically warn against this misuse in the case of lead.

Second, one can also predict the growth of a tendency to use biological indicators as a substitute for rather than (as suggested by ACGIH) a supplement to airborne exposure limits. Ontario's Ministry of Labour has claimed that evidence of satisfactory protection of workers from the effects of airborne lead is provided by blood lead levels within the limits prescribed by regulation even though permissible airborne concentrations are being greatly exceeded (125, 126). Thus whatever safety factors (if any) are built into the permissible exposure limits for airborne contaminants may be effectively neutralized. Yet variability of individual uptake and response is only one among many rationales for the use of safety factors.

Biological monitoring: some further implications *continued*

Finally, a shift in emphasis in the setting of permissible levels from environmental to biological bases may lend added credibility to the continuation of the human experiment. This problem, which is analogous in some respects to the erosion or elimination of safety factors, is suggested by two recent articles, although many others could probably be found.

The first reports on the development of sets of behavioral tests "which would facilitate monitoring individuals exposed to neurotoxins in the workplace" in conjunction with an exposure index such as blood lead levels or environmental monitoring. Administration of these tests, which are sugested as a way of detecting (for example) early effects of exposure to lead and organic solvents, "has been accomplished on plant premises by trained technicians in a period of less than 40 minutes." (127) But once the effects are detected, what then?

The second article reports on the use of biological monitoring as an early warning of possible exposure to carcinogens. Despite the high correlation between mutagenicity in *in vitro* tests and carcinogenicity in one or more laboratory species:

> "[E]xtrapolation of results from bacterial test systems to the human species is a giant step which most scientists are unwilling to take, but human genetic monitoring of exposed populations can provide essential information to confirm or deny evidence of an effect on the human genetic system. The enlightened occupational physician will recognize the need to provide definitive answers regarding genetic effect in humans exposed to compounds judged to be positive in the *in vitro* mutagenic test systems." (128, p. 248)

Noting the scientific literature linking increased human cancer incidence and increased chromosome damage as detected in cytogenetic studies, the author argues for expanded monitoring of exposed workers to detect genetic injury, as a way of avoiding the uncertainties of extrapolating from animal experiments and *in vitro* tests to human experience. "Cytogenetics...shows great promise in helping to identify human carcinogens through the utilization of this practical clinical test system in man himself." Identification, however, is not the same as prevention of the type which is made possible by the presumption that carcinogenicity in non-human test systems should be taken as evidence of human carcinogenicity.

In both examples, the focus has shifted (at least in the first instance) from preventing adverse health effects to detecting them, on either an individual basis (in the case of neurotoxins) or a group basis (in the case of cytogenetic monitoring). The underlying question of standard-setting (that of the criterion for acceptable or tolerable

Biological monitoring: some further implications *continued*

risks) is resolved implicitly in recommendations such as those quoted. The attempt to achieve greater precision and reduce scientific uncertainty is pursued by conducting what amount to human experiments.

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